4-1-2008

Part I: Studies toward the total synthesis of Trocheliophorolide A. part II: Studies on the development of a palladium-catalyzed carbonylative cross-coupling towards the synthesis of alkenyl alkynyl ketones

William T. Spencer

Part I: Studies Toward the Total Synthesis of Trocheliophorolide A.
Part II: Studies on the Development of a Palladium-Catalyzed Carbonylative Cross-Coupling Towards the Synthesis of Alkenyl Alkynyl Ketones.

William T. Spencer III

Submitted in Partial Fulfillment

of the

Requirements for the Degree

Master of Science in Chemistry

Supervised by

Dr. Christina Collison

Department of Chemistry

The College of Science

Rochester Institute of Technology

Rochester, New York

2008

Approved: Christina G. Collison, Ph.D.
Project Advisor

L. Paul Rosenberg, Ph.D.
Department Head

Copyright Release Form

Part I: Studies Toward the Total Synthesis of Trocheliophorolide A.
Part II: Studies on the Development of a Palladium-Catalyzed Carbonylative Cross-Coupling Towards the Synthesis of Alkenyl Alkynyl Ketones.

Signature

Date

Acknowledgements

Foremost, I would like to sincerely thank my research advisor, Dr. Christina Collison, for all of the support, encouragement, teaching, mentoring, and friendship she has given me throughout my education at RIT. The endless, enthusiastic help and support she has afforded me goes far beyond what I ever could have imagined or expected from a research advisor. I would also like to extend my gratitude to Dr. Morrill, Dr. Smith, Dr. Rosenberg, Dr. O'Handley, and Dr. Kim for their substantial advice and assistance throughout my graduate career.

My deep thanks to Dr. Brian Bliss, Dr. Michael Guaciaro, Dr. James Schulte, Dr. Feryan Ahmed, and Dr. Christopher Cioffi, all former mentors at AMRI. All of these individuals have taught, encouraged, and supported me, and without their help, I never would have made it this far.

I would also like to thank my mother, Linda Spencer, my father, William Spencer Jr., and my late grandfather, John Pappas for all of the emotional and financial support they have given me during my undergraduate years at RPI and my graduate years at RIT.

Lastly, I would like to thank the RIT chemistry department for their significant financial support in the form of a tuition waiver, and teaching and research assistantships, throughout my education at RIT.

Abstract

In Part I, efforts toward the total synthesis of a novel antibacterial γ-lactone, Trocheliophorolide A, are described. The natural product was isolated from Red Sea soft corals *S. trocheliophorum* and *L. arboreum*. Biological assays show that this compound exhibits significant growth inhibition of bacterial cell lines *S. aureus* and *B. subtilis*. The structure consists of an *(S)*-β-angelica lactone ring connected to an ynediene side chain.

Our strategy employs synthesis of the lactone ring as a stannylfuranone, which will be Stille coupled with vinylidene dibromide to form an alkenyl bromide. This alkenyl bromide will be cross-coupled with an enynyl metal species to install the remainder of the sidechain, affording the target natural product. The stannylfuranone ring was constructed using a tandem palladium-catalyzed hydrostannation-lactonization protocol.

In Part II, a study towards the synthesis of alkenyl alkynyl ketones via a novel palladium-catalyzed carbonylative cross-coupling reaction of alkynyl halides and alkenylstannanes is discussed. Initial efforts have focused on optimization of the direct cross-coupling of the two components in the absence of carbon monoxide pressure antecedent to development of the carbonylative coupling reaction.

Abbreviations

AcCl	acetyl chloride
AcOH	acetic acid
AD mix α	asymmetric dihydroxylation mixture α
AIBN	azobisisobutyronitrile
Bu	butyl
t-Bu	*tert*-butyl
n-BuLi	*n*-butyllithium
t-BuLi	*t*-butyllithium
t-BuOH	*n*-butanol
Bn	benzyl
Cp	cyclopentadiene
CSA	camphorsulfonic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD	diethylazodicarboxylate
DIBAL-H	diisobutylaluminum hydride
Diglyme	bis(2-methoxyethyl) ether
DMA	dimethylacetamide
DMF	dimethyl formamide
DMAP	4-dimethylamino pyridine
DMSO	dimethylsulfoxide
Et	ethyl

EtOH	ethanol
EtOAc	ethyl acetate
Et_3N	triethylamine
Et_2NH	diethylamine
g	gram(s)
GC-MS	gas chromatograph–mass spectrometer
h	hour(s)
hex	hexanes
HF • pyr	hydrogen fluoride–pyridine complex
HMPA	hexamethylphosphoramide
Hz	hertz
KHMDS	potassium hexamethyldisilazide
KOAc	potassium acetate
LDA	lithium diisopropylamide
2,6-Lutidine	2,6-dimethylpyridine
L	ligand
m-CPBA	*meta*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MeOH	methanol
MMPP	magnesium monoperoxyphthalic acid
MOM	methoxymethyl
m.p.	melting point

Ms	methanesulfonyl
MsCl	methanesulfonyl chloride
NaHMDS	sodium hexamethyldisilazide
NaOAc	sodium acetate
NMM	*N*-methylmorpholine
PCC	pyridinium chlorochromate
$PdCl_2(PPh_3)_2$	dichlorobis(triphenylphosphine)palladium (II)
$Pd_2(dba)_3$	tris(dibenzylideneacetone)dipalladium (0)
$PdCl_2(MeCN)_2$	dichlorobis(acetonitrile)palladium (II)
$Pd(PPh_3)_4$	tetrakis(triphenylphosphine)palladium (0)
Ph	phenyl
PivCl	pivalyl chloride
PMB	*para*-methoxybenzyl
PPh_3	triphenylphosphine
PPTS	pyridinium-*p*-toluenesulfonate
Pyr	pyridine
Red-Al	sodium bis(2-methoxyethoxy)aluminum hydride
RT	room temperature
$RuCl_2(PPh_3)_3$	dichlorotris(triphenylphosphine)ruthenium (II)
SEM	2-(trimethylsilyl)ethoxymethyl
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
THF	tetrahydrofuran

THP	tetrahydropyranyl
TLC	thin layer chromatography
Tf_2O	trifluoromethane sulfonic anhydride
TMS	trimethylsilyl
Tr	triphenylmethyl
TrCl	chlorotriphenylmethane
Ts	*para*-toluenesulfonyl
p-TSA	*para*-toluenesulfonic acid
p-TsCl	*para*- toluenesulfonyl chloride
VAZO-88®	1,1′-azobis(cyclohexanecarbonitrile)

Table of Contents

Part I: Studies Toward the Total Synthesis of Trocheliophorolide A

Part II: Studies on the Development of a Palladium-Catalyzed Carbonylative Cross-Coupling Towards the Synthesis of Alkenyl Alkynyl Ketones.

List of Schemes

List of Figures

List of Tables

Part I: Studies Toward the Total Synthesis of Trocheliophorolide A.

1.0 Introduction and Background

The objective of this project is to synthesize Trocheliophorolide A, a novel butenolide natural product. Upon completion the compound will be furnished to Professor Michael Savka of the RIT Biology Department for further biological evaluation.

1.1 Isolation and Biological Activity of Trocheliophorolide A

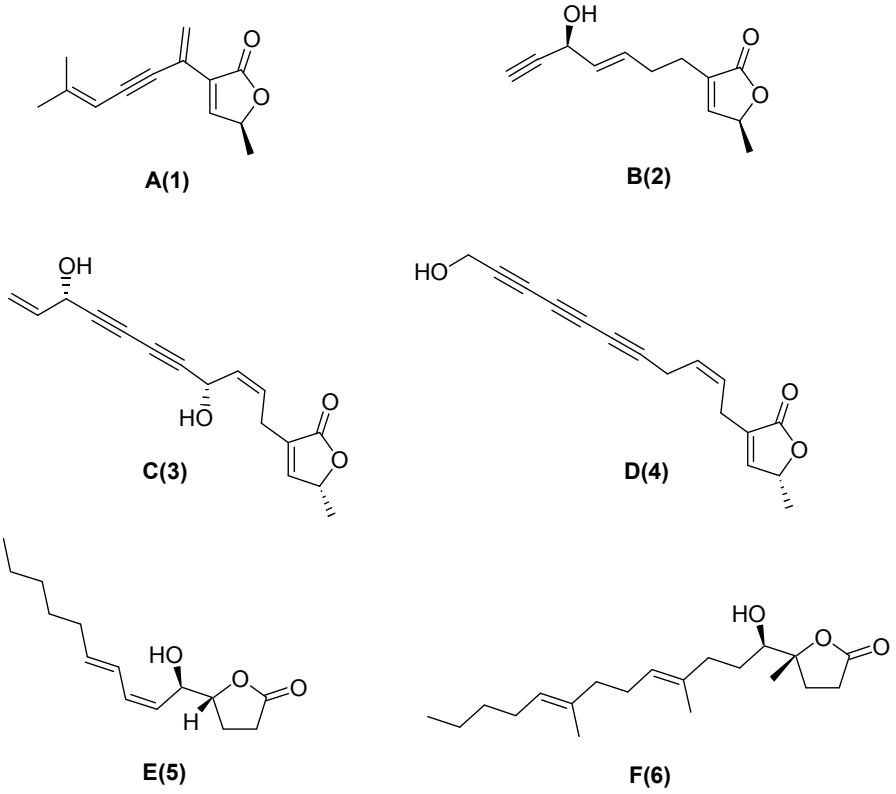
Soft corals have been the source of dozens of natural products, primarily steroids and their derivatives[1,2]. Fatty acid derivatives are less known[3], although more than 30 years ago, butenolide lipids were isolated from *Pterogorgia anceps* and *Pterogorgia guadalupensis*[2,4-6], and recently several terpenoid fatty acids were isolated from *Nephthea chabrolii*[7]. Several years ago[8], six unique butenolide and butanolide lipids (Figure 1) possessing rare unsaturation patterns were isolated from soft corals *Sarcophyton trocheliophorum* and *Lithophyton arboretum*, collected in the gulf of Aqaba of the Red Sea. Many natural products[9] and natural aroma components[10] possess such butenolide units. Biological evaluation of these lactones showed that they have antibacterial activity against two bacterial cell lines, and toxicity against brine shrimp *Artemia salina* (Table 1[8]). The *(S)*-butenolides seemed to exhibit somewhat higher activity. To date, their molecular mode of action is unknown.

Table 1. Bioactivities of Trocheliophorolides A-F (**1**-**6**).

Test organism	**1**	**2**	**3**	**4**	**5**	**6**
Staphylococcus aureus[a]	11.5	13.2	8.5	10.3	7.8	18.6
Bacillus subtilis[a]	13.0	14.9	7.6	13.9	5.6	14.7
Artemia salina[b,c]	8.3	61.5	0.8	3.2	15.3	21.4

[a] Samples (10 μg) were applied on 50.8 mm paper disks, values are in diameters (mm) of inhibitory zones. [b] In μg mL^{-1} (minimum lethal doses). [c] The sample (~0.05 mg) was dissolved in 50 μL of DMSO and added to a test vial of artificial seawater (3.0 mL). Approximately 20 brine shrimp, *Artemia salina*, were added to the vial. The brine shrimp were observed periodically over a 24 h period. A positive assay was the death of all brine shrimp.

Figure 1. Molecular Structures of Trocheliophorolides A-F.



1.2 Biological Significance of *(S)*-β-Angelica Lactone Natural Products

(5S)-5-methyl-5*H*-furan-2-one, more commonly known as *(S)*-β-Angelica lactone (**7**, Figure 2) is a type of butenolide (**8**, Figure 2). A butenolide is a γ-lactone ring possessing a single element of unsaturation. Butenolides are also referred to as 2-furanones since they are oxidized derivatives of furans. They are ubiquitous in nature, and are common structural elements of natural products synthesized by biochemical pathways in organisms[11]. The vast majority of butenolide-containing natural products either exhibit some kind of biological activity or are potent flavor and aroma components[10,12]. *(S)*-β-angelica lactone natural products, in particular the annonaceous acetogenin[13,14] class of natural products, encompass a broad array of antibacterial, antitumor, anthelminitic, antimalarial, antiprotozoal, pesticidal, herbicidal, fungicidal, cancerostatic, and anticarcinogenic agents[13-17].

Figure 2. Molecular Structures of (*S)*-β-Angelica Lactone (**7**) and Butenolide (**8**).

7 **8**

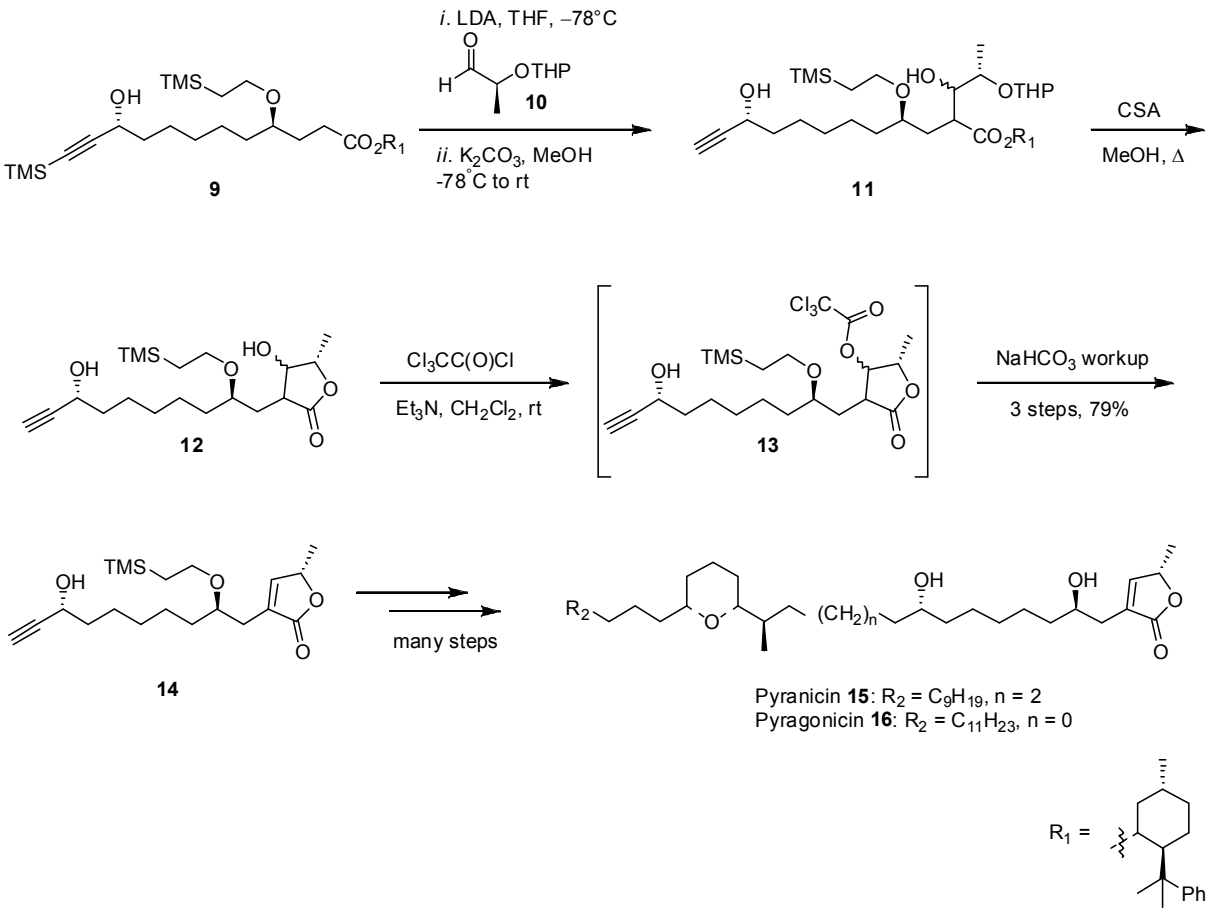
1.3 Previous Synthetic Approaches to the *(S)*-β-Angelica Lactone Ring in Natural Products

Dozens of natural products and their derivatives containing the *(S)*-β-Angelica lactone ring have been synthesized in the past several decades[13,14]. Construction of the lactone ring has been accessed via a number of commonly used synthetic approaches.

1.3.1 Synthesis of the Lactone Ring Using *(S)*-Lactal

An approach that has been heavily used for the past ten years involves the crossed aldol reaction of an ester with THP-protected *(S)*-lactal, followed by lactonization, and finally elimination of a leaving group at the α- or β- position of the lactone ring to afford the butenolide. A recent example of this strategy was used by Strand[18] in the syntheses of pyranicin (**15**) and pyragonicin (**16**) (Scheme 1).

Scheme 1. Synthesis of the Butenolide Fragment of Pyranicin and Pyragonicin from *(S)*-Lactal.



Ester **9** was converted to adduct **11** via crossed aldol reaction with THP-protected *(S)*-lactal (**10**) using LDA as the base. The THP group was removed with camphorsulfonic acid and heat, which under the same conditions, induced transesterification to the methyl ester and subsequent ring closure to hydroxylactone **12**. Subsequent conversion of the hydroxyl group of the lactone to a trichloroacetoyl group gave intermediate **13**, which was worked up with sodium bicarbonate to afford the butenolide fragment **14** in 79% yield over 3 steps. Butenolide **14** was then converted to Pyranicin (**15**) and Pyragonicin (**16**) after multiple steps. This approach was also used in previous syntheses of pyranicin[19,20] and pyragonicin[20], as well as syntheses of AA005[21], Annonacin[22], Asimin[23], (+)-Bullaticin[24], Cyclogoniodenin T[25], Goniocin[25], (+)-Longicin[26], Longimicin C[27], Mucocin[28,29], Muconin[30,31], Muricatetrocin C[32,33], Pseudoannonacin A[34], Rollidecins C

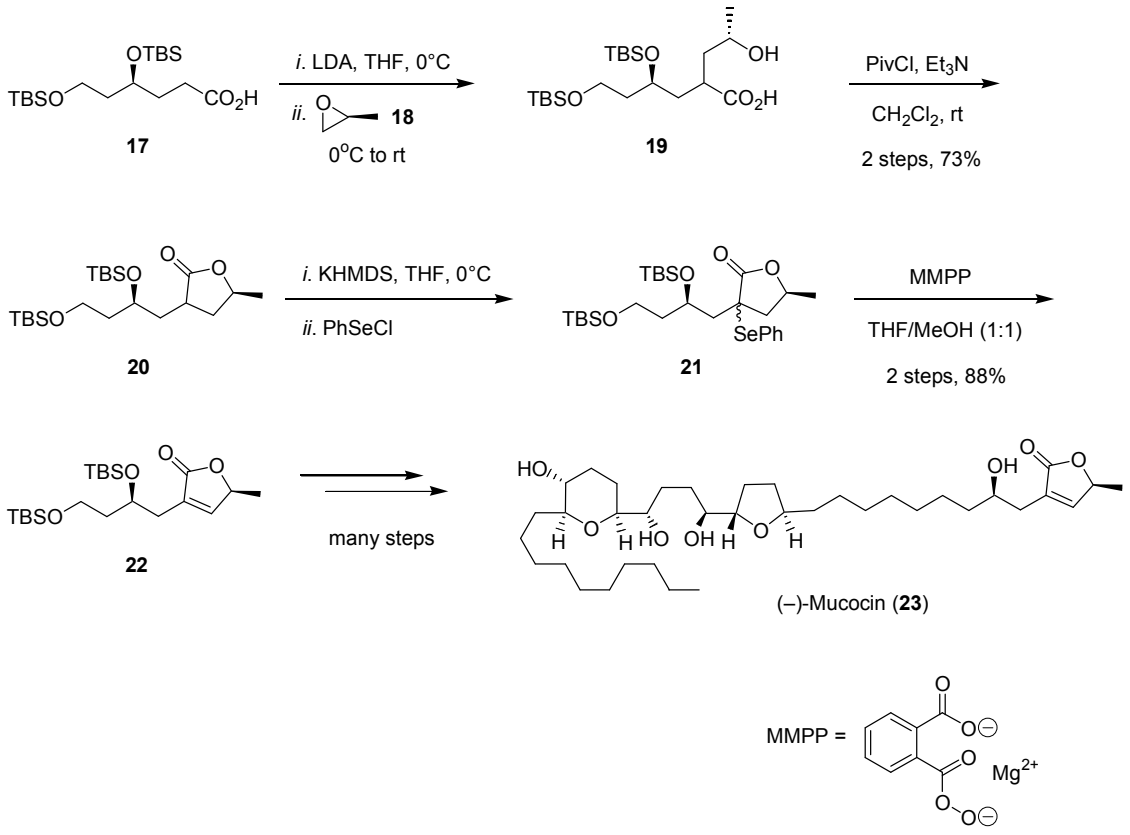
and D[35], Squamotacin[36], Tonkinecin[22], and various other annonaceous acetogenin analogues[15,33,37-45].

One of the limitations of this method is that a methylene carboxylic acid ester unit must be built into the intermediate prior to conversion to the butenolide ring. Another is the need to protect the *(S)*-lactal prior to its installation into the substrate, which adds an additional two steps to the synthesis. A further issue is that camphorsulfonic acid, in addition to inducing the desired THP deprotection and ring closure, may also cause other unwanted lactonization reactions, deprotections, and isomerizations of unsaturated systems in the intermediate. Lastly, the use of trichloroacetyl chloride poses a chemoselectivity problem in the presence of other nucleophilic functional groups in the substrate, such as other hydroxyl groups and amino groups, which would require protection to prevent their acylation.

1.3.2 Synthesis of the Lactone Ring Using *(S)*-Propylene Oxide

Another approach that has been used involves the treatment of a carboxylic acid enolate with *(S)*-propylene oxide, esterification of the carboxyl group, lactonization of the hydroxyester to the lactone, and elimination of a leaving group at the α- or β- position, which is either present in masked form in the carboxylic acid starting material or installed subsequently, to afford the furanone. A prototypical example of this approach was used by Koert[46] in a synthesis of (–)-Mucocin (Scheme 2).

Scheme 2. Synthesis of the Butenolide Fragment of (–)-Mucocin from *(S)*-Propylene Oxide.



Intermediate carboxylic acid **17** was converted to its enolate with LDA, and then treated with *(S)*-propylene oxide (**18**) to yield hydroxyacid **19**. Acid **19** was esterified with pivaloyl chloride to the corresponding hydroxyester, which underwent lactonization to **20**. Lactone **20** was enolized with KHMDS, and then subjected to phenylselenium chloride to give selenide **21**. Selenide **21** was oxidized with magnesium monoperoxyphthalate and subsequently underwent a retro hetero-ene reaction to give butenolide fragment **22** in 73% yield over 2 steps. **22** was then converted to (–)-Mucocin (**23**) after multiple steps. This approach and some variations have also been used in another synthesis of (–)-Mucocin[47], as well as syntheses of Asimicin[48-50], Asimin[49], Asiminocin[49], Bullanin[49], Bullatacin[48,50,51], Bullatanocin[52], Jimenezin[53], Longimicin D[54], Mosin B[55,56], Membranacin[57], (+/–)-Muconin[58], (+)-Muconin[59], Mucoxin[60], Murisolin[61-63], Pyragonicin[64], Reticulatacin[65,66], Reticulatamol[67], Rollicosin[68], Rollimembrin[57], Rolliniastatin 1[57,69], Solamin[65,66,70], Squamocin A and D[71,72], (+)-Squamostanal-A[73],

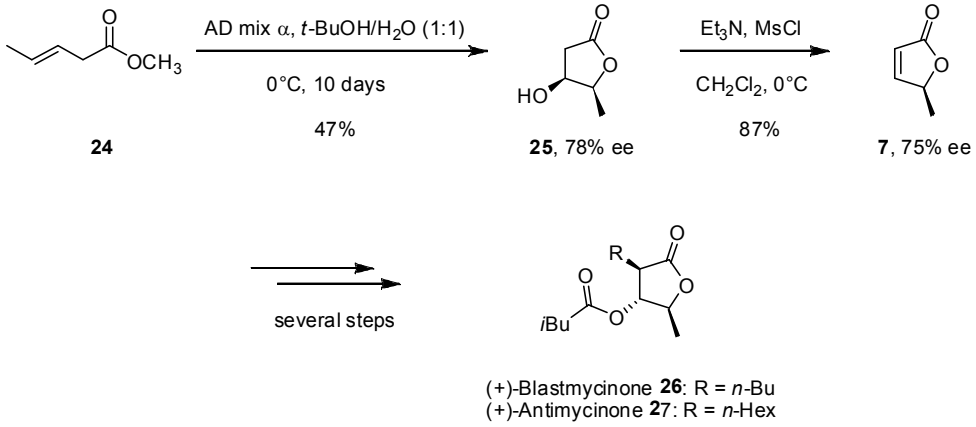
Squamostolide[74], Tonkinelin[75], Trilobacin[76], Uvaracin[77], Uvigrandin A[78], and various analogues of the annonaceous acetogenins[79-96].

One obvious limitation of this method is that the substrate must possess a methylenecarboxylic acid unit. Another is that the required formation of an enolate for both the *(S)*-propylene oxide installation and the phenylselenium chloride substitution use lithium diisopropylamide and potassium hexamethyldisilazide, both very strong bases which may deprotonate other acidic protons in the molecule. Lastly, the use of MMPP as an oxidant poses a chemoselectivity problem in the presence of other groups susceptible to oxidation by this reagent, including olefins and aromatic aldehydes[97].

1.3.3 Synthesis of the Lactone Ring via Sharpless Asymmetric Dihydroxylation

A unique and concise approach to the β-angelica lactone ring employs the Sharpless asymmetric dihydroxylation to produce a diastereomerically enriched diol, which undergoes lactonization. Conversion of the hydroxyl group to a leaving group and subsequent elimination affords the butenolide ring. This approach was exploited by Bruckner[98] in the syntheses of (+)-Blastmycinone and (+)-Antimycinone (Scheme 3).

Scheme 3. Synthesis of the Butenolide Intermediate of (+)-Blastmycinone and (+)-Antimycinone via Sharpless Dihydroxylation.



Commercially available β, γ-unsaturated ester **24** was asymmetrically dihydroxylated and lactonized using asymmetric dihydroxylation mixture α over 10 days to produce

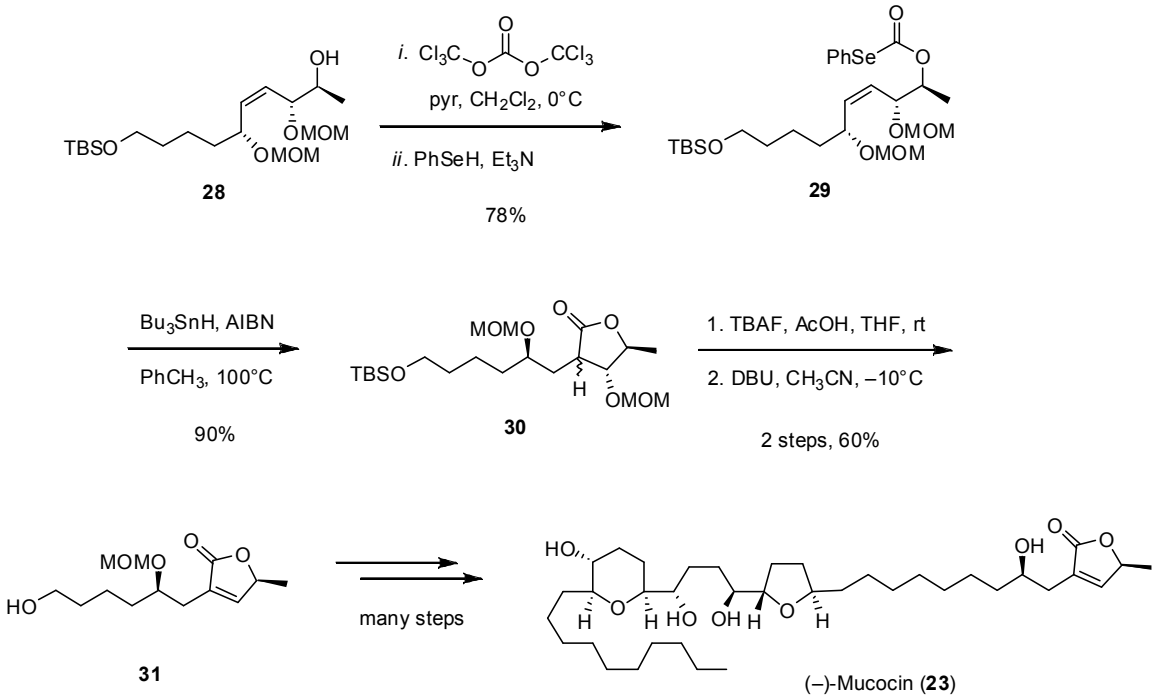
hydroxylactone **25** in 47% yield and 78% ee. The hydroxyl group was mesitylated and subsequent elimination afforded *(S)*-β-angelica lactone **7** in 87% yield and 75% ee. After several more steps, (+)-Blastmycinone (**26**) and (+)-Antimycinone (**27**) were obtained. Although the dihydroxylation step affords the desired isomer in relatively low yield, the synthesis overall was a higher yielding and more concise route to both *(S)*-β-angelica lactone and the target molecules than other available methods. This approach was also used in the synthesis of (+)-Montecristin[99] and a trio of mosquito-larvicidally active annonaceous acetogenins[45,100].

A major limitation of the asymmetric dihydroxylation route is that the starting β, γ-unsaturated ester is unstable and may undergo isomerization to the α, β-unsaturated ester. In addition, the lactonization step takes 10 days to drive to completion and is low-yielding.

1.3.4 Synthesis of the Lactone Ring via Free Radical Cyclization and Elimination

An approach less frequently exploited involves the free radical cyclization of a selenocarbonate, followed by an elimination. Takahashi[101] used this approach in a synthesis of (–)-Mucocin (Scheme 4).

Scheme 4. Synthesis of the Butenolide Fragment of (–)-Mucocin via Free-Radical Cyclization.



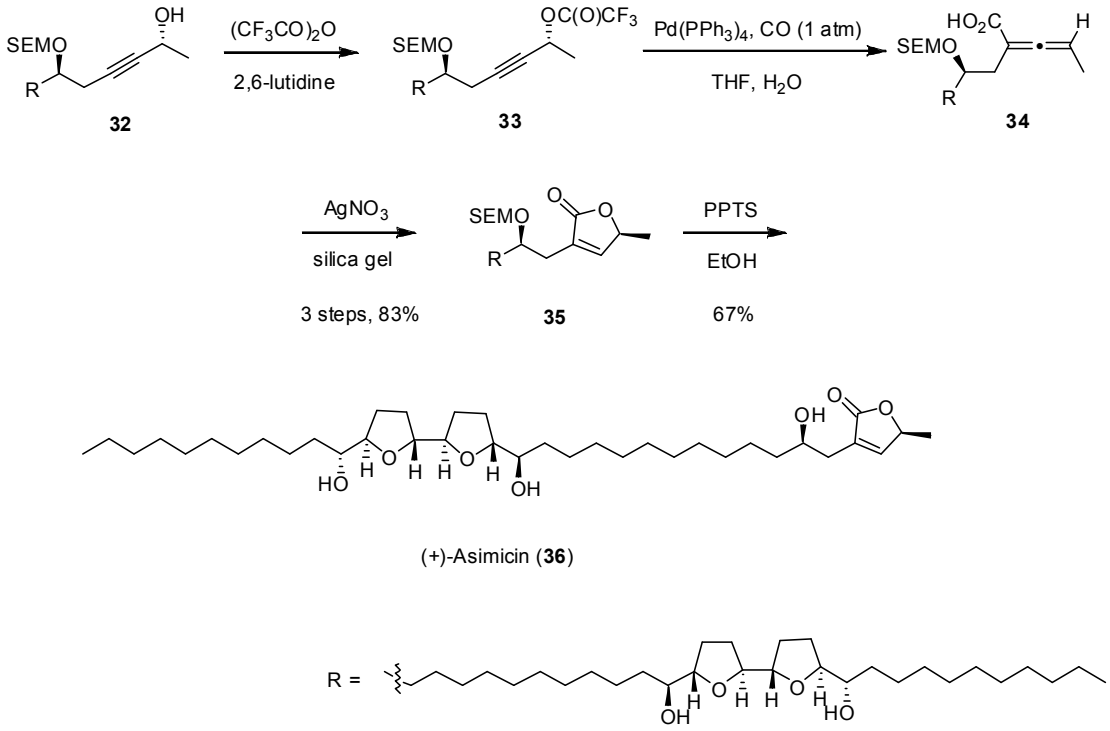
Alcohol **28** was acylated with triphosgene in pyridine, then treated with benzeneselenol to provide selenocarbonate **29** in 78% yield. A free radical cyclization using tributyltin hydride and azobisisobutyronitrile in toluene at 100°C afforded lactone **30** in 90% yield, which was then deprotected with tetrabutylammonium fluoride and eliminated with 1,8-diazabicyclo[5.4.0]undec-7-ene to provide butenolide **31** in 60% yield over both steps. Butenolide **31** was then further elaborated to provide (–)-Mucocin (**23**). This approach has also been used in two other syntheses of (–)-Mucocin[102,103].

A drawback of this method is that the starting substrate must be a homoallylic alcohol with a leaving group on the carbon adjacent to the double bond. This is a complex structural element which requires multiple steps to synthesize. The use of triphosgene[104] to acylate the hydroxyl group presents a toxicity hazard, as well as a chemoselectivity problem due to its extremely high reactivity. Finally, the successful use of free radical chain chemistry using AIBN and tributyltin hydride can sometimes be precluded by slow propagation step(s), which can result in termination and therefore low yields.

1.3.5 Synthesis of the Lactone Ring via Silver (I)-Promoted Allenic Acid Cyclization

An elegant approach to the butenolide ring developed by Marshall and coworkers[105] in the synthesis of (+)-Asimicin employed a palladium(0)-catalyzed hydroxycarbonylation to produce an allenic acid, followed by a silver(I)-promoted cyclization to afford the butenolide ring (Scheme 5).

Scheme 5. Synthesis of the Butenolide Ring of (+)-Asimicin via Allenic Acid Cyclization.



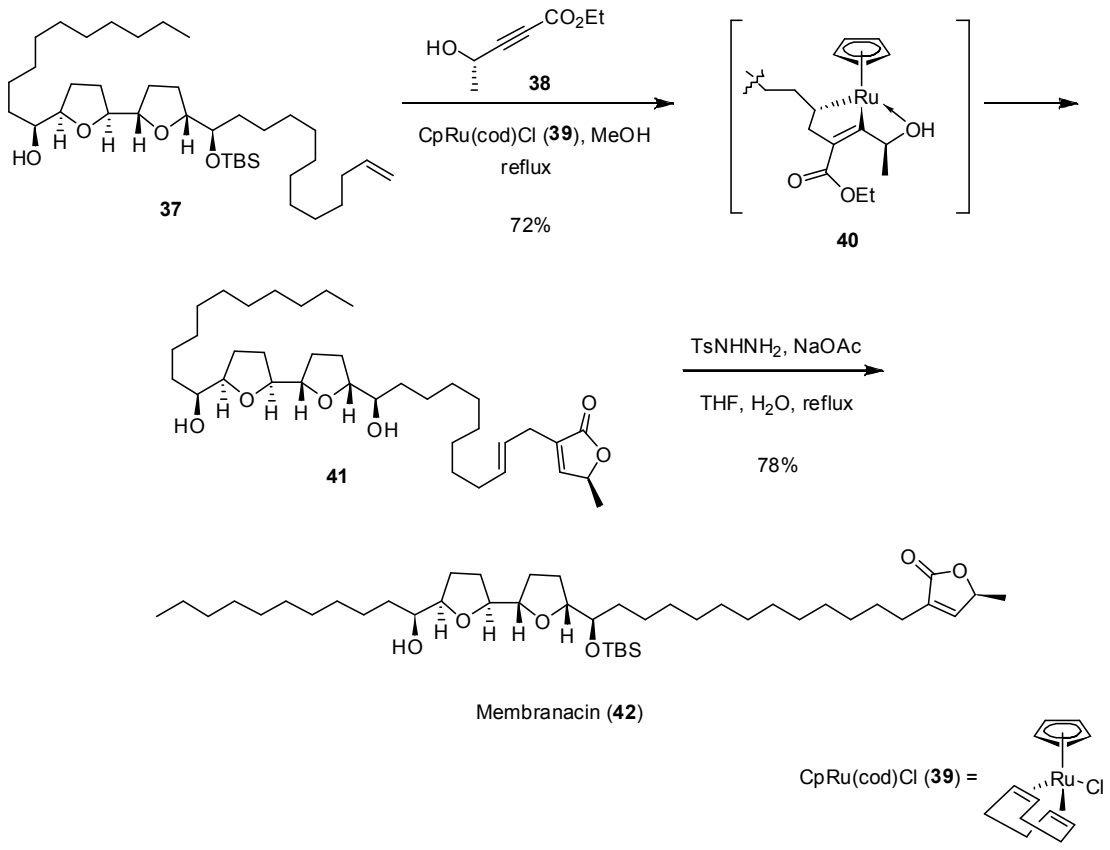
Propargyl alcohol **32** was trifluoroacetylated using trifluoromethane acetic anhydride in 2,6-lutidine to provide **33**. Carbonate **33** was carboxylated under an atmosphere of carbon monoxide in THF and water, catalyzed by tetrakistriphenylphosphine palladium(0), to give allenic acid **34**. Acid **34** was cyclized with silver (I) nitrate to afford butenolide **35** in 83% over 3 steps, which was finally deprotected to give (+)-Asimicin (**36**) in 67% yield. The same approach was utilized in another synthesis of Asimicin[106], and syntheses of Asiminecin[107], Asiminocin[107], (30S)-Bullanin[108], and (+)-Bullatacin[109].

The main drawback of this method lies in the relative instability of allenes. The presence of a carboxyl group on the allene moiety further increases its reactivity, particularly the electrophilicity of the distal allenic carbon atom. This instability is the basis for the functionality's facile electrocyclization under such incredibly mild conditions.

1.3.6 Synthesis of the Lactone Ring via the Trost Ruthenium-Catalyzed Alder-Ene Ynoate Annulation

Trost and coworkers[110] developed a method for synthesizing α,γ-substituted butenolides using a ruthenium-catalyzed Alder-ene reaction[111-113] of an alkene and a hydroxyalkynoate, which has been widely used in the synthesis of various natural products containing butenolide rings. A recent example of this strategy was used by Brown and coworkers[114] in a synthesis of Membranacin (Scheme 6).

Scheme 6. Synthesis of the Butenolide Fragment of Membranacin via Trost Alder-Ene Ynoate Annulation.



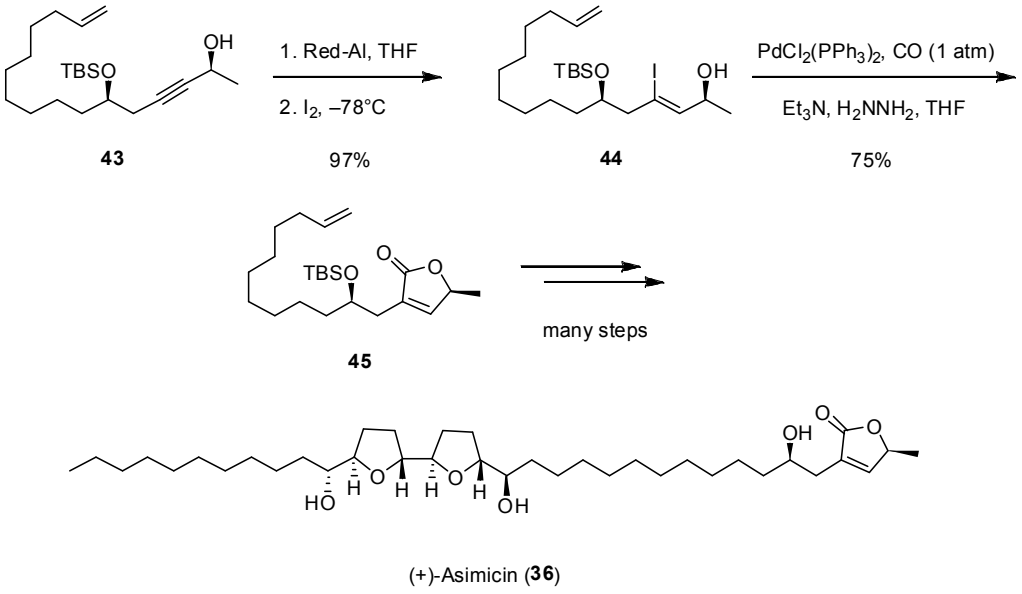
Alkene intermediate **37** was subjected to a Ru-catalyzed Alder-ene reaction with hydroxyalkynoate **38** in methanol under reflux to provide butenolide **41** in 72%. The reaction hypothetically proceeds through metallacycle **40**, which yields a hydroxyalkenoate that subsequently lactonizes under thermal conditions. Saturation of the double bond with tosyl hydrazine, sodium acetate, water, and THF under reflux yielded Membranacin (**42**) in 78% yield. This protocol has been employed in syntheses of (+)-Ancepsenolide[110], (+)-*5S*-Hydroxyparviflorin[115], (+)-Parviflorin[115], (+)-Solamin[116], (+)-Squamocin K[115], and various derivatives of the annonaceous acetogenins[117-123].

The drawback of this method is the need to reflux the olefin under the Alder-ene reaction conditions, which poses a risk for unwanted side reactions or decomposition of the substrate.

1.3.7 Synthesis of the Lactone Ring via Carbonylation

Synthesis of the butenolide ring of several natural products has been accomplished by the intramolecular carbonylation of a 1-iodo-2-methylenehydroxy olefin. Marshall and coworkers[124] exemplified this approach in a synthesis of Asimicin (Scheme 7).

Scheme 7. Synthesis of the Butenolide Fragment of Asimicin via Carbonylation.



Propargyl alcohol intermediate **43** was hydroaluminated with Red-Al in THF, then iodinated to afford allyl alcohol **44** in 97% yield. **44** was carbonylated under a carbon monoxide atmosphere catalyzed by *trans*-dichlorobis(triphenylphosphine) palladium (II) in triethylamine, hydrazine, and THF in 75% yield to provide butenolide **45**, which after further elaboration gave (+)-Asimicin (**36**). Carbonylation methodologies have been used in another synthesis of (+)-Asimicin[125] in addition to syntheses of (+)-Bullatacin[125], (+)-Gigantecin[126], (+)-Hamabiwalactone B[127], (+)-Parviflorin[128], and derivatives of annonaceous acetogenins[126,129,130].

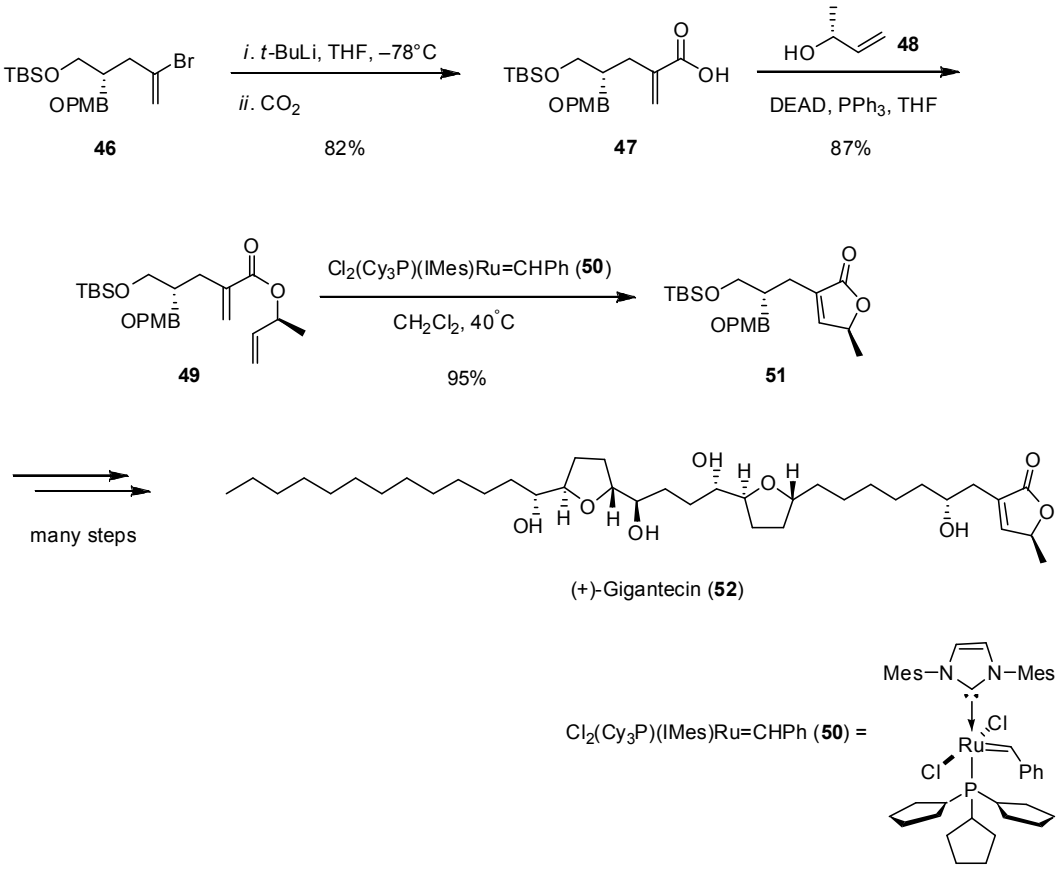
A drawback of this method is the need to synthesize an intermediate possessing a 1*S*-methyl propargyl alcohol moiety. Additionally, the regioselectivity of the hydroalumination-iodination must be very high in order to install the iodine on the carbon atom of the double bond distal to the hydroxyl group, in order to make the butenolide

ring; steric hindrance near this position may preclude dominant formation of this isomer and therefore the ability to form the butenolide ring.

1.3.8 Synthesis of the Lactone Ring via Ring-Closing Metathesis

An approach that has seen use in recent years has been ring-closing metathesis of an α,β-unsaturated propenyl ester. Crimmins[131] used this approach in a synthesis of (+)-Gigantecin (Scheme 8).

Scheme 8. Synthesis of the Butenolide Fragment of (+)-Gigantecin via Ring-Closing Metathesis.



Vinyl bromide **46** was lithium-halogen exchanged using *t*-BuLi in THF at –78°C, then put under a carbon dioxide atmosphere to afford the carboxylate, which after aqueous workup gave vinylogous carboxylic acid **47** in 82% yield. A Mitsunobu coupling with alcohol **48** using diethylazodicarboxylate and triphenylphosphine in THF gave ester **49** in

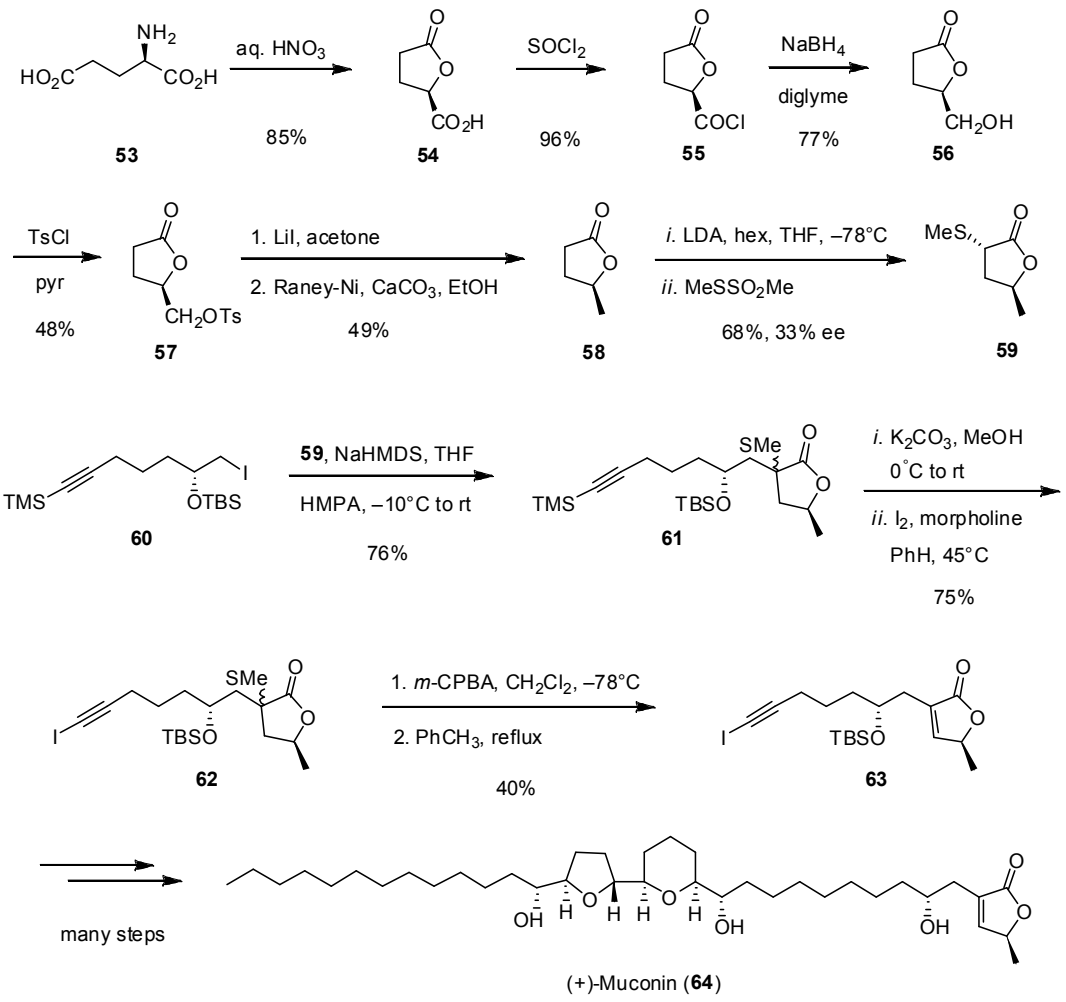
87% yield. A ring-closing olefin metathesis was performed on **49** using catalyst **50** in methylene chloride to give butenolide fragment **51**. A number of further transformations afforded (+)-Gigantecin (**52**). The ring-closing metathesis strategy has also been used in the synthesis of *S,S*-(+)-Dehydrohomoancepsenolide[132] and a synthesis of (–)-Mucocin[133].

A major shortcoming of this method is the need to perform a lithium-bromide exchange on the alkenyl bromide; besides its handling dangers, *tert*-butyllithium is an extremely strong base which can effect undesired deprotonations of kinetically reactive alkenyl and aryl protons in other regions of the substrate. Another pitfall is the possibility of a "lithium-halogen dance", a cascade of sequential deprotonation–halogen exchange reactions which result in the most stable organolithium species[134].

1.3.9 Synthesis of the Lactone Ring From D-Glutamic Acid

This approach involves the separate synthesis of a thiomethylated lactone via a precedented procedure[135-137], its installation into an intermediate of the natural product via the enolate, and subsequent elimination to afford the angelica lactone ring. This approach is demonstrated in Kitahara's[138] synthesis of (+)-Muconin (Scheme 9).

Scheme 9. Synthesis of the Butenolide Fragment of (+)-Muconin from D-Glutamic Acid.



D-glutamic acid **53** was dehydrated with nitrous acid to produce lactone **54** in 85% yield, which was converted to its acid chloride **55** in 96% yield using thionyl chloride. **55** was reduced to alcohol **56** using sodium borohydride in diglyme, and then tosylated with *p*-toluenesulfonyl chloride in pyridine to give tosylate **57** in 48% yield. Tosylate **57** was converted to the corresponding iodide via a Finkelstein reaction with lithium iodide followed by a Raney-nickel reduction to give methylated lactone **58** in 49% across both steps. Lactone **58** was then converted to its enolate with lithium diisopropylamide, then to methyl sulfide **59** with methyl methanethiolsulfonate. Sulfide **59** was converted again to its enolate with sodium hexamethyldisilazide and treated with iodide **60**, which underwent an S_N2 substitution to give adduct **61** in 76% yield. Lactone **61** was TMS-

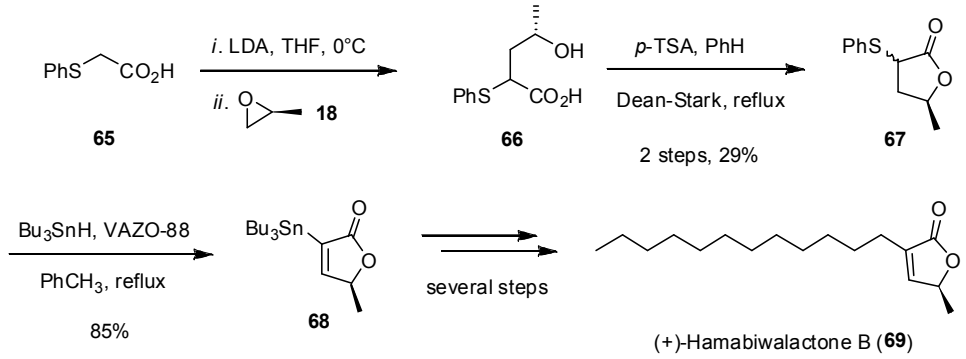
deprotected with potassium carbonate in methanol, and iodinated with iodine to give propargyl iodide **62** in 75% yield. Iodide **62** was converted to the corresponding sulfone using *meta*-chloroperoxybenzoic acid, then refluxed in toluene to give the butenolide elimination product **63** in 40% yield across both steps. (+)-Muconin (**64**) was synthesized from **63** after several more steps. This method has been used in two other syntheses of (+)-Muconin[139,140], the synthesis of Acaterin[137], and a synthesis of Squamostolide[141].

An obvious and significant shortfall of this approach is the sheer number of steps required to synthesize the thiomethylated lactone, install it into the alkyl iodide, oxidize the thiomethyl group to a sulfone, then perform the elimination. Furthermore, the overall yield of the lactone synthesis prior to its installation into the substrate is an unacceptably low 10%, and after taking the installation, oxidation and elimination steps into account for this particular case, results in an extremely low 3% yield. As a result, this method is likely the most limited and least desirable one available.

1.3.10 Synthesis of the Lactone Ring as a Stannylfuranone

Another convenient approach to the synthesis of butenolide-containing natural products and precursors involves the synthesis of the butenolide fragment as a stannylfuranone for subsequent metal-catalyzed cross-coupling. To date, two methods have been developed to synthesize the stannylfuranone. The first method, used by Sweeney[142,143] and coworkers in the synthesis of (+)-Hamabiwalactone B, is somewhat similar to the method described in Section 1.3.2, except the last step involves a direct interconversion of the thiophenyl group to a tributylstannyl group (Scheme 10).

Scheme 10. Synthesis of the Stannylfuranone from *(S)*-Propylene Oxide.

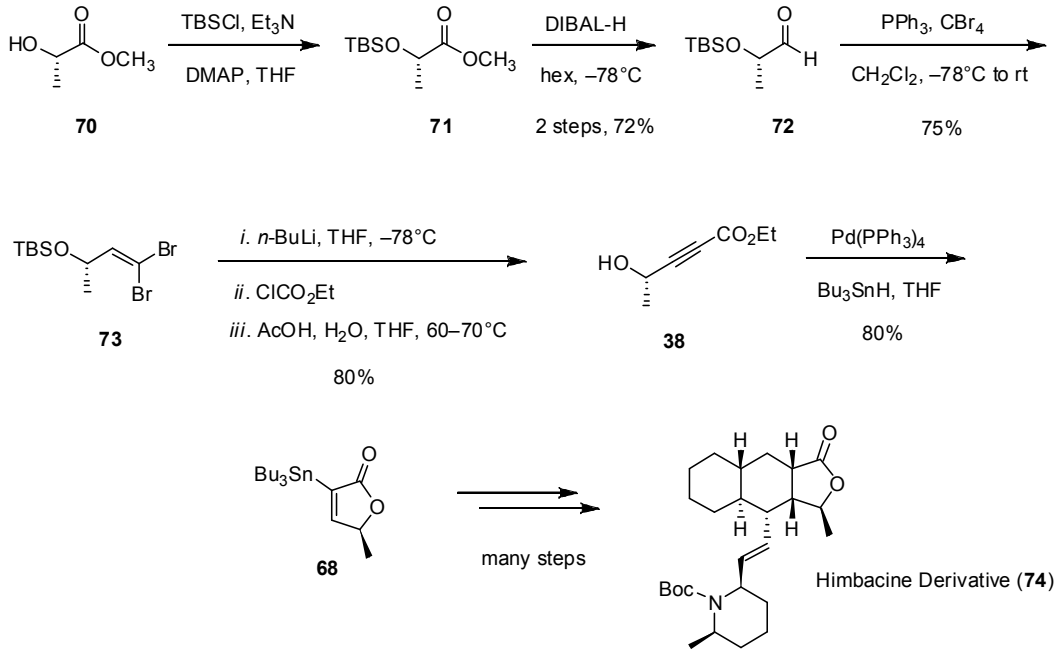


Thiophenylacetic acid **65** was converted to its lithium enolate with LDA, followed by addition of *(S)*-propylene oxide (**18**). The resulting hydroxyacid **66** was then lactonized using *p*-toluenesulfonic acid in toluene under reflux to afford lactone **67** in 29% yield over 2 steps. **67** was then converted to stannylfuranone **68** in 85% yield using tributyltin hydride and VAZO-88® as the free radical initiator. After several more steps, (+)-Hamabiwalactone B (**69**) was afforded.

One drawback of this synthesis is the extremely low yield of the first two steps; it can be assumed that the epoxide ring opening step had a very low regioselectivity, contributing to the low yield. Additionally, *(S)*-propylene oxide is an unnatural compound which, whether purchased commercially or freshly synthesized, must be purified via chiral chromatography. The approach is therefore neither a chiral pool nor an asymmetric synthesis. All of these considerations make the overall synthesis unelegant.

Another approach to stannylfuranone **68** employed by Hofman[144] and coworkers in their synthesis of Himbacine derivatives involves the hydrostannation of a hydroxyalkynoate[110], which subsequently lactonizes (Scheme 11).

Scheme 11. Synthesis of the Stannylfuranone via Hydrostannation.



Commercially available *(S)*-ethyl lactate **70** was TBS-protected to give silyl ether **71**, then DIBAL-H reduced to aldehyde **72** in 72% yield over both steps. Aldehyde **72** was converted to gem-dibromide **73** in 75% yield via a Corey-Fuchs olefination using triphenylphosphine and carbon tetrabromide in dichloromethane at –78°C. Dibromide **73** was doubly eliminated using *n*-butyllithium in THF at –78°C to the corresponding alkynyllithium, quenched with ethyl chloroformate to give the alkynoate, and worked up with aqueous acetic acid and THF under heat to remove the TBS group, all in 80% yield. A hydrostannation was then performed on the resulting alkynoate (**38**), using tributyltin hydride and tetrakistriphenylphosphine palladium(0) catalysis in THF to afford stannylfuranone **68** in 80% yield. **68** was further elaborated to give Himbacine derivative **74**.

The main drawback of this synthesis is the use of gem-dibromoolefin **73** as the intermediate prior to elimination. These compounds are notoriously unstable, and therefore have an extremely short shelf life.

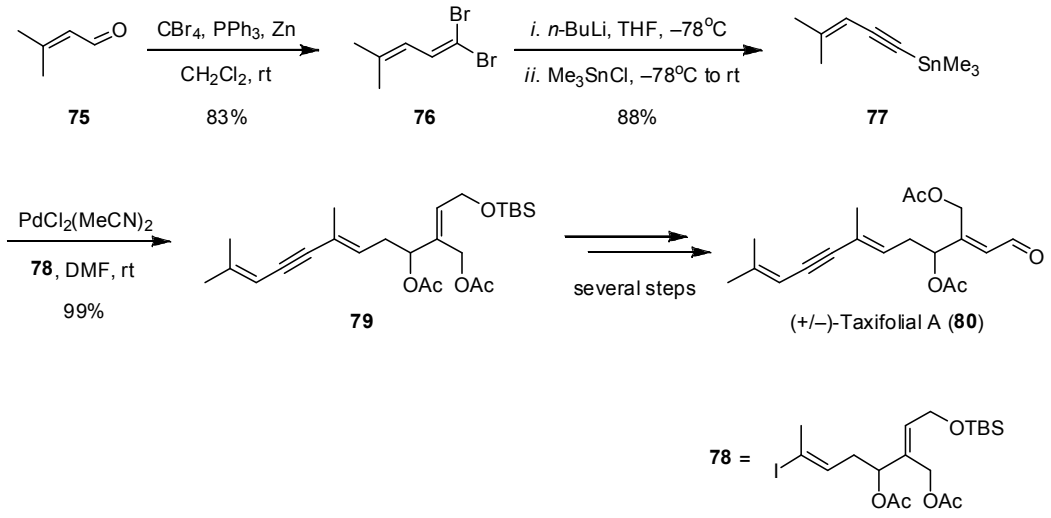
1.4 Previous Synthetic Approaches to the Ynediene Appendage in Natural Products

The only other biologically active natural products that possess the ynediene chain are those of the cytotoxic Caulerpenyne family[145-149]. Additionally, advanced intermediates containing the chain have also been synthesized.

1.4.1 Synthesis of the Ynediene Chain via Stille Cross-Coupling

The only published approach to the chain's assemblage in the Caulerpenynes involves the synthesis of an enynyl stannane, and its Stille cross-coupling to a vinyl halide. This approach is shown in the Commeiras[150] synthesis of (+/–)-Taxifolial A (Scheme 12).

Scheme 12. Synthesis of the Ynediene Appendage of (+/–)-Taxifolial A.



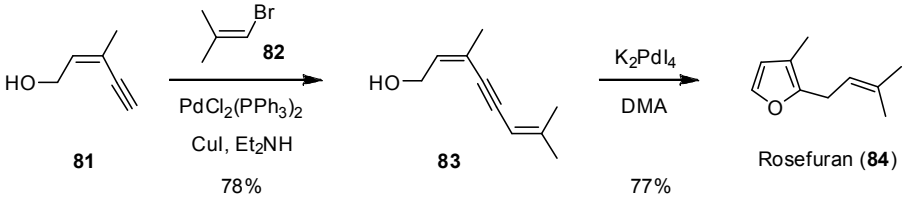
Commercially available crotonaldehyde derivative **75** was converted to dibromide **76** in 83% yield via a Corey-Fuchs reaction using carbon tetrabromide, triphenylphosphine, and zinc in dichloromethane. Dibromide **76** then underwent elimination at –78°C with *n*-BuLi and subsequent lithium-bromide exchange to the corresponding alkynyllithium, then quenched with trimethyltin chloride to give enynyl stannane **77** in a yield of 88%. Stannane **77** was then efficiently Stille cross-coupled with alkenyl iodide **78** to give ynediene **79** in 99% yield, which was then elaborated after several more steps to afford (+/–)-Taxifolial A (**80**). This approach has also been used in another synthesis of (+/–)-Taxifolial A[151] and the synthesis of other Caulerpenyne family members, namely (+/–)-

Caulerpenyne[151,152], (+/–)-*iso*-Caulerpenyne[150,151], (+)-Furocaulerpin[153], and (–)-Furocaulerpin[151,153,154].

1.4.2 Synthesis of the Ynediene Chain via Sonagashira Coupling

Salerno[155] and Marshall[156] both used a Sonagashira coupling to synthesize the ynediene intermediate in their syntheses of Rosefuran (Scheme 13).

Scheme 13. Synthesis of the Ynediene Intermediate of Rosefuran.



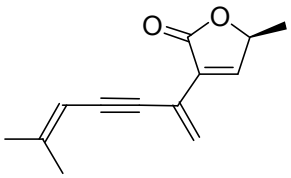
Commercially available enynol **81** was cross-coupled with vinyl bromide **82** using *trans*-dichlorobis(triphenylphosphine) palladium(II), copper (I) iodide, and diethylamine to give ynediene **83** in 78% yield. This was then cycloisomerized to Rosefuran (**84**) in 77% yield using palladium (II) iodide, potassium iodide, and *N,N*-dimethylacetamide.

2.0 Synthetic Design

2.1 Retrosynthetic Analysis of Trocheliophorolide A

As shown in Figure 3, Trocheliophorolide A (**1**) contains an *(S)*-β-angelica lactone ring connected at the α-carbon to an unusual ynediene side chain.

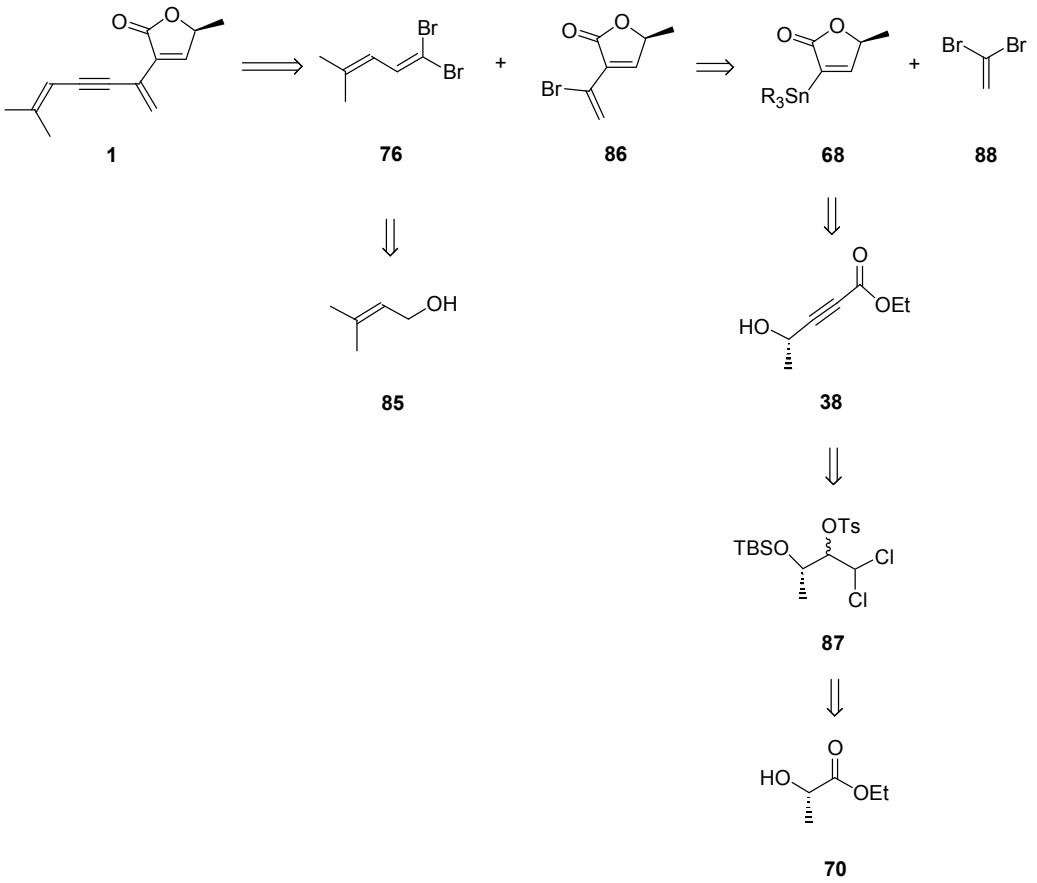
Figure 3. Molecular structure of Trocheliophorolide A.



1

Our retrosynthetic strategy is outlined in Scheme 14. The natural product can be constructed using a Stille or Negishi cross-coupling of alkenyl bromide **86** with an *in situ* generated alkynylmetal species of gem-dibromoolefin **76**. The dibromoolefin is accessed from allyl alcohol **85**. Alkenyl bromide **86** can be derived from a Stille coupling of stannylfuranone **68** and vinylidene dibromide **88**. Stannylfuranone **68** can be obtained from a precursor alkynoate **38**, which could be accessed from tosylate intermediate **87**. Tosylate **87** can be synthesized from commercially available *(S)*-ethyl lactate **70**.

Scheme 14. Retrosynthetic Analysis of Trocheliophorolide A.



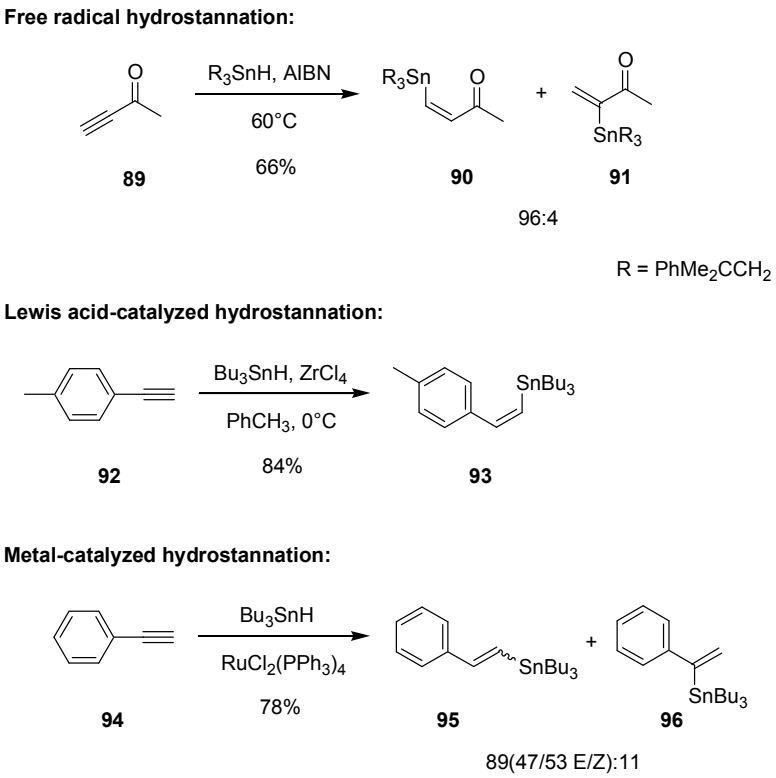
There are several distinct advantages to our method of incorporating the *(S)*-β-angelica lactone ring into natural products via stannylfuranone **68** over the methods discussed in Section 1.3. The main benefit is that it can be installed via a simple Stille cross-coupling at any point in a synthesis to obtain a variety of complex systems. Since the ring is constructed separately prior to installation into a system, all of the conditions used in its construction do not have to be adapted or altered to accommodate the presence of functional groups or other structural features unique to that system. In addition, it is stable, has a long shelf life, and can be synthesized on a large scale. Its attractiveness is enhanced by virtue of its derivation from an inexpensive, naturally-derived starting material that is commercially available and chiral, so its enantiomer can be synthesized simply by starting the synthesis with *(R)*-ethyl lactate instead of the *(S)*-enantiomer.

An advantage of our particular synthetic route over those discussed in Section 1.3.10 is that it is a chiral pool approach and therefore more elegant when contrasted with Sweeney's[142,143], which was neither regioselective nor derived from a chiral pool. It is also higher yielding than his approach. Another advantage is that our route proceeds through the highly stable, storable tosylate intermediate **87** instead of the unstable gem-dibromoolefin **73** used by Hofman[144].

2.2 Synthetic Strategy: Construction of Stannylfuranone 68

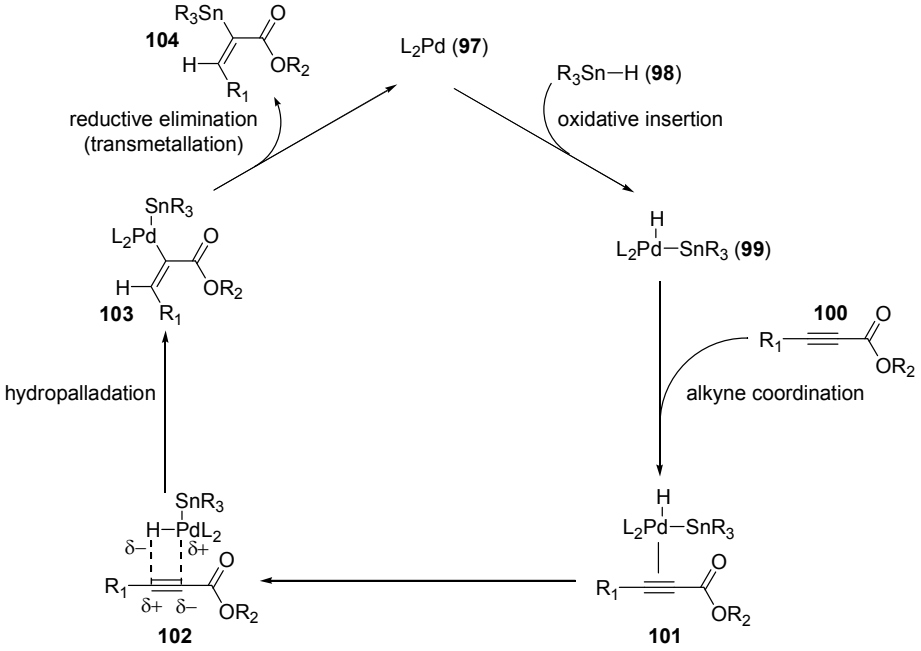
The hydrostannation reaction is the addition of a trialkyltin hydride across a double or triple bond. The hydrostannation reaction is a common method of producing a stannane coupling partner for a Stille cross-coupling reaction. It can proceed through a radical mechanism[157-161], in which addition of the trialkylstannyl and hydrido substituents add anti to the olefin or acetylene, through a Lewis acid-catalyzed mechanism[162], which also gives the anti product, or through a metal-catalyzed mechanism[163-169], which gives the syn product. Scheme 15 shows examples of each of these approaches.

Scheme 15. Conditions Used in the Hydrostannation Reaction.



In the case of the palladium-catalyzed hydrostannation of an alkynoate[164,168], the trialkyltin hydride adds syn across the triple bond of an alkynoate to regioselectively produce an *(E)*-α-stannyl enoate, generating the *(E)*-β-stannyl enoate as a minor product. The mechanism of this reaction (Scheme 16) is not well understood, and has been proposed based on observed products and analogy with other related reactions[168].

Scheme 16. Proposed Mechanism of Alkynoate Hydrostannation.



R, R_1, R_2 = Alkyl groups

The first step in the catalytic cycle is the oxidative insertion of a 14-electron palladium(0) complex (**97**) into the the trialkyltin hydride Sn-H bond to form palladium(II) complex **99**. Coordination of alkynoate **100** ensues, followed by alignment of the partially negative α-carbon of the alkynoate with partially positive palladium, and the partially positive β-carbon of the alkynoate with the partially negative hydrido ligand. Migratory insertion then occurs to form alkenylpalladium complex **103**. Reductive elimination follows to regenerate complex **97** while forming alkenylstannane **104**.

3.0 Results and Discussion

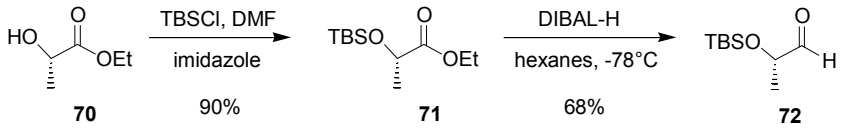
3.1 Synthesis of Stannylfuranone 68

Following our retrosynthetic analysis, we started our synthesis of the stannylfuranone using commercially available *(S)*-ethyl lactate which conveniently possessed the chiral center of our target molecule.

3.1.1 Synthesis of TBS-Protected α-Hydroxy Aldehyde 71

(S)-ethyl lactate (**70**) was TBS-protected using *tert*-butyldimethylsilyl chloride and imidazole in *N,N*-dimethylformamide to cleanly provide silyl ether **71** in 90% yield[170] (Scheme 17). The ethoxycarbonyl group of **71** was reduced to give aldehyde **72**[170] in 68% yield after distillation using diisobutylaluminum hydride in hexanes at –78°C.

Scheme 17. Synthesis of TBS-Protected α-Hydroxy Aldehyde **72**.

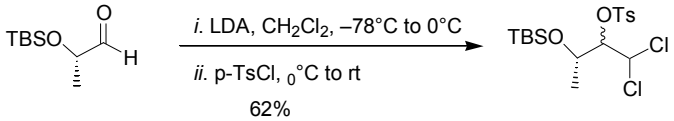


70 **71** **72**

3.1.2 Synthesis of Tosylate 87

Aldehyde **72** was then treated with an *in situ*-generated dichloromethane anion to give the tetrahedral lithium alkoxide followed by trapping with *p*-toluenesulfonyl chloride to give tosylate **87**[170] (Scheme 18).

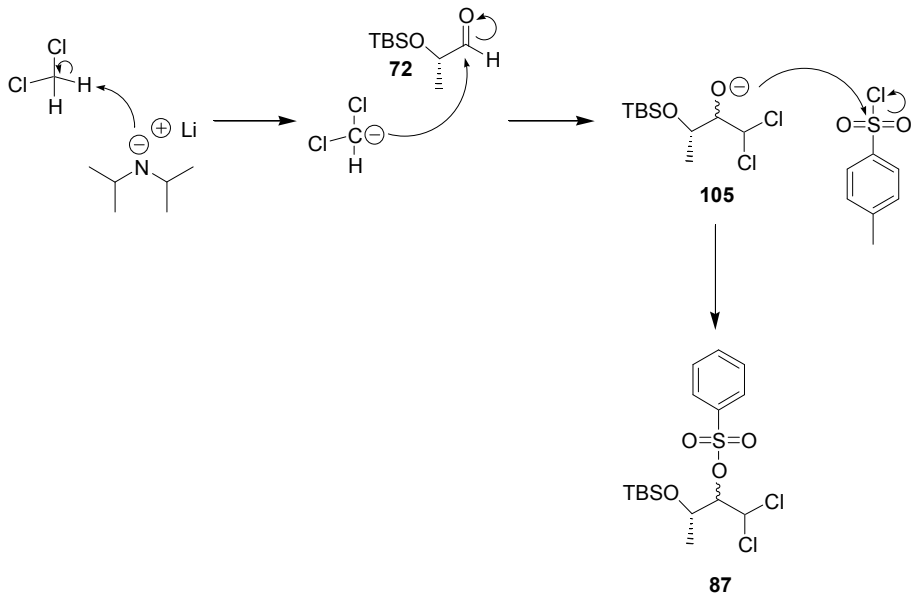
Scheme 18. Synthesis of Tosylate **87**.



72 **87**, 10% de

This reaction proceeds via a nucleophilic addition mechanism, as illustrated in Scheme 19.

Scheme 19. Mechanism of Tosylation.



Fresh lithium diisopropylamide is added to dichloromethane, and deprotonates it to generate its anion. The anion nucleophilically adds to the carbonyl group of **72** to give alkoxide intermediate **105**. **105** attacks *p*-toluenesulfonyl chloride, displacing the chloride ion to give tosylate **87**.

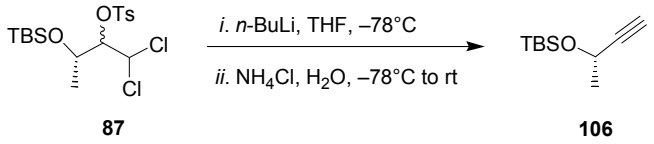
The reaction is quite impure, with a main side product being the adduct formed by addition of the dichloromethane anion to *p*-toluenesulfonyl chloride. Chromatography of **87** needed to be performed slowly, and since several minor impurities that are undetectable by TLC are present, fractions needed to be tested by H^1 NMR before combining. The reaction yield is 62% after calculating the impurities out of the crude H^1 NMR, and is a 55:45 mixture of diasteromers.

3.1.3 Synthesis of Alkynoate 108

Our next priority was to convert tosylate **87** to its corresponding terminal alkyne via an elimination reaction, then react it to form an ethyl alkynoate. Crude tosylate **87** was treated with 3.3 equivalents of *n*-butyllithium to make the alkynyllithium, which was quenched with aqueous ammonium chloride to generate terminal alkyne **106** (Scheme

20). The reaction gave a complex mixture of products containing a tiny amount of **106**. Volatility of **106** was also suspected.

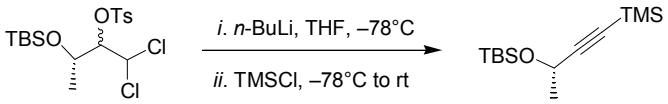
Scheme 20. Synthesis of Terminal Alkyne **106**.



87 **106**

To determine whether the elimination was occurring, crude tosylate **87** was converted to the alkynyllithium with *n*-butyllithium as before, but the acetylide was instead quenched with trimethylsilyl chloride to make TMS-protected alkyne **107** (Scheme 21). The reaction proceeded in 23% yield from aldehyde **72**.

Scheme 21. Synthesis of TMS-Protected Alkyne **107**.

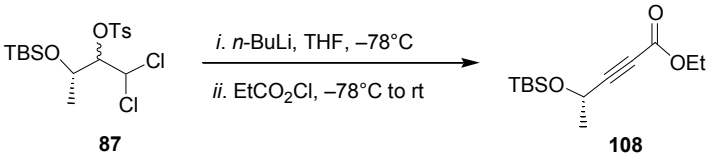


87 **107**

We concluded that the elimination worked, and that the yield would likely improve in an analogous elimination–trapping to directly furnish alkynoate **108** in a one-pot transformation.

We proceeded to repeat the reaction using pure tosylate and quenched the alkynyllithium with distilled ethyl chloroformate to give alkynoate **108** (Scheme 22).

Scheme 22. Synthesis of Alkynoate **108**.



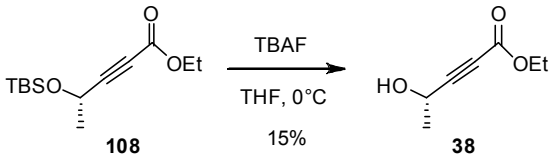
87 **108**

If the ethyl chloroformate is not distilled, the crude product has to be chromatographed before bringing to the deprotection step. The only impurities in the crude were ethyl chloroformate and ethylcarbonic acid.

3.1.4 Synthesis of γ-Hydroxy Alkynoate 38

After obtaining our alkynoate, our next objective was to remove the TBS group in order to perform the final hydrostannation-lactonization step. Initial studies tested the effectiveness of tetrabutylammonium fluoride as a desilylating agent (Scheme 23).

Scheme 23. TBAF Deprotection of Alkynoate **108**.

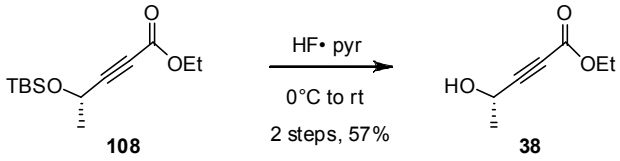


108 **38**

The reaction was performed using pure **108** in THF at 0°C, and the product alcohol was attained in an unacceptable 15% yield after preparative thin layer chromatography. Multiple unidentified side products were also isolated. Whenever the reaction was performed using impure **108**, only a tiny amount of product was generated, and was inseparable from impurities.

We then explored the feasibility of using hydrogen fluoride–pyridine complex (Scheme 24).

Scheme 24. Hydrogen Fluoride–Pyridine Deprotection of Alkynoate **108**.



108 **38**

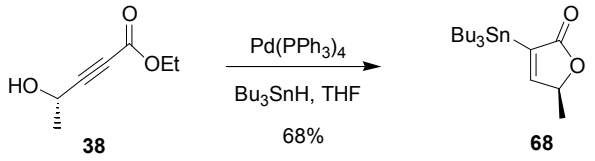
The deprotection was performed at 0°C in THF, and it was necessary to use at least 16 equivalents of HF•pyridine to drive the reaction to completion. The product mixture, although not particularly dirty, required chromatographic purification for the

hydrostannation step. The isolated yield was 57% across 3 steps, from pure tosylate **87**. The alcohol **38** starts to decompose after 1-2 weeks at 0°C. Crude alkynoate **108** can also be used in the reaction with no detrimental effect on percent conversion or ease of purification.

3.1.5 Hydrostannation to Stannylfuranone 68

With the hydroxyalkynoate in hand, we proceeded to the final hydrostannation step[144] (Scheme 25). A solution of **38** and freshly made tetrakistriphenylphosphine palladium(0) in THF was subjected to a dropwise addition of tributyltin hydride in THF, which, after workup and chromatography, afforded stannylfuranone **68** in 68% yield.

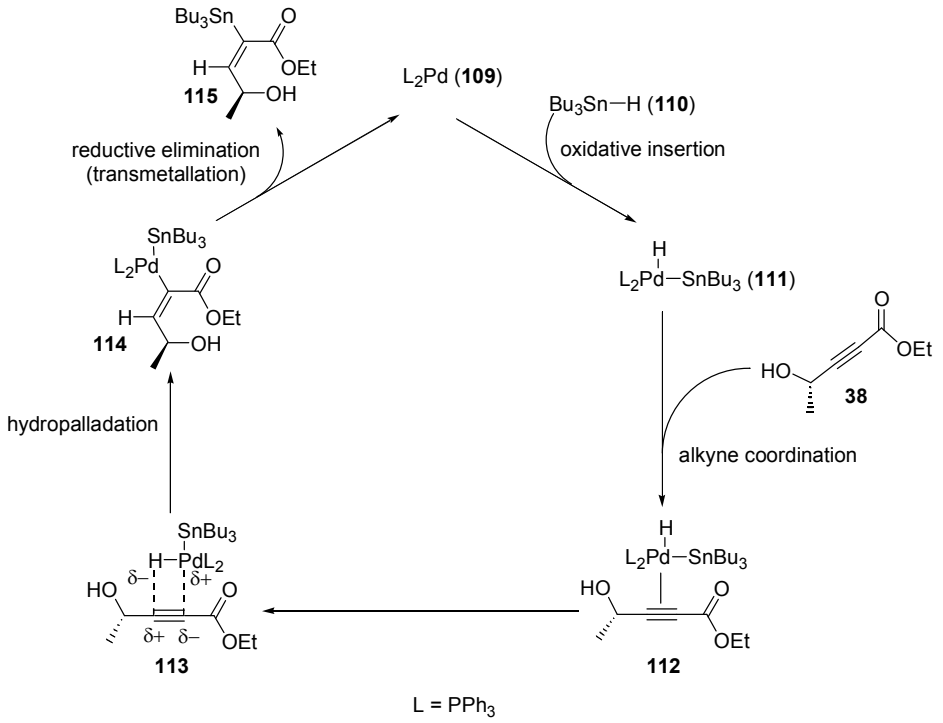
Scheme 25. Hydrostannation to Stannylfuranone **68**.



A minor product is the β-stannylated lactone. Earlier studies showed that *in situ* generation of the Pd-catalyst before addition of **38** and tributyltin hydride affords the product in 12% yield, so the catalyst must be separately made.

The proposed mechanism[168] of the reaction is depicted in Scheme 26. The first step is

Scheme 26. Proposed Mechanism of Hydrostannation to Produce Precursor to Stannylfuranone **68**.



oxidative insertion of the bis(triphenylphospine) palladium(0) complex (**109**) into the tin-hydrogen bond of tributyltin hydride (**110**) to form complex **111**. Hydroxyalkynoate **38** then coordinates to the palladium to form complex **112**. This is followed by alignment of the partially negative α-carbon of the alkynoate with partially positive palladium, and the partially positive β-carbon of the alkynoate with the partially negative hydrido ligand. Subsequent migratory insertion then occurs to form alkenylpalladium intermediate **114**. Reductive elimination affords the product alkenylstannane **115** while regenerating the catalyst. Alkenylstannane **115** undergoes lactonization to form the stannylfuranone (**68**).

3.2 Synthetic Studies Toward the Stille Cross-Coupling Partner

Our earliest work towards synthesizing Trocheliophorolide A involved constructing the entire ynediene side chain of the natural product as a coupling partner for direct Stille cross-coupling with the stannylfuranone. Current efforts are focused on coupling the

stannylfuranone with vinylidene dibromide, then using the resulting alkenyl bromide in a final Stille coupling with an enynylmetal species to complete Trocheliophorolide A.

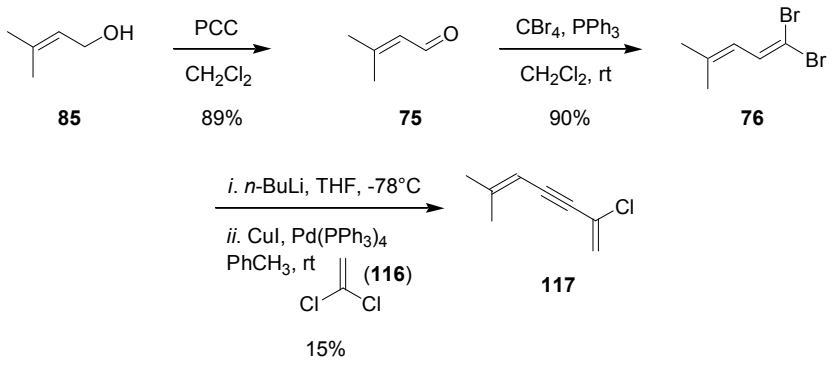
3.2.1 Chloroynediene Coupling Partner 117

The first ynediene coupling partner we attempted to make was a chloroynediene. Studies towards the synthesis of the chloroynediene[171] focused on two approaches: one utilizing an *in situ* elimination-Sonogashira coupling, and the other a Stille coupling.

3.2.1.1 Via *In Situ* Elimination–Sonogashira Coupling

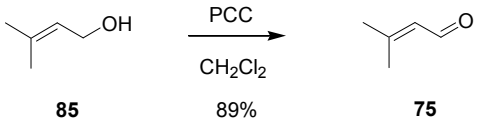
This approach begins with commercially available 3-methyl-2-buten-1-ol (**85**), which is oxidized to aldehyde **75** using pyridinium chlorochromate (Scheme 27). The aldehyde is subjected to a Corey-Fuchs reaction to give dibromoolefin **76**, which is then subjected to a one-pot elimination–lithium-bromide exchange–Sonogashira coupling to provide chloroynediene **117**.

Scheme 27. Elimination–Sonogashira Coupling Route Toward Chloroynediene **117**.



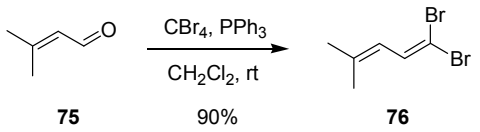
The oxidation of alcohol **85** to aldehyde **75** was performed using pyridinium chlorochromate in methylene chloride and resulted in a 89% yield[172] (Scheme 28). Although the byproduct chromium (IV) salt is extremely difficult to remove completely from the crude product, a filtration through florisil followed by a second filtration through silica gel removed the vast majority. Aldehyde **75** is suspected to be volatile as yields have varied over multiple attempts using the same procedure. Several attempts to make **75** via manganese (II) oxide oxidation resulted in low yields.

Scheme 28. Synthesis of 3-Methyl-2-Butenal **75**.



Aldehyde **75** was then converted to dibromoolefin **76** via a Corey-Fuchs reaction[173] using carbon tetrabromide and triphenylphosphine in methylene chloride (Scheme 29).

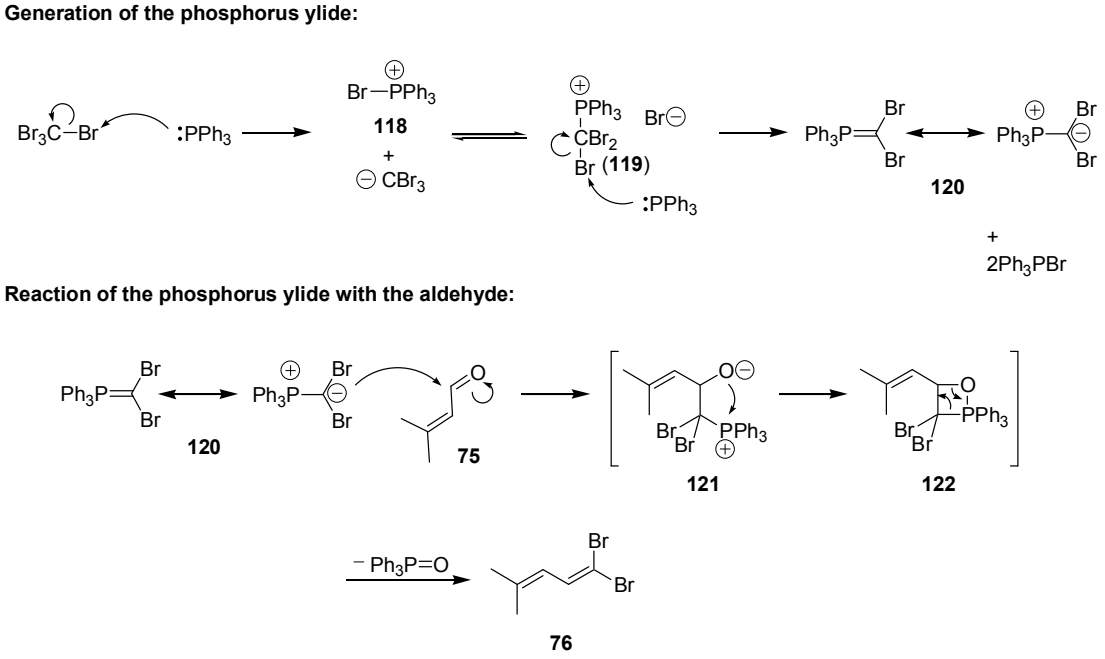
Scheme 29. Synthesis of Dibromoolefin **76**.



It was found that the use of zinc, often used to promote the reaction and increase yields, actually had the opposite effect in our case, and was therefore not used in later reactions. The highest yields and most pure material was obtained when aldehyde **75** was purchased commercially instead of synthesized, presumably because of the presence of the byproduct chromium salt from the PCC oxidation of alcohol **85**.

The mechanism of the Corey-Fuchs reaction[174] is illustrated in Scheme 30, and is analogous to that of the Wittig reaction. First, triphenylphosphine abstracts a bromine atom from carbon tetrabromide. This forms a bromophosphonium salt (**118**), which is in equilibrium with the triphenyl tribromomethyl phosphonium bromide salt (**119**). Triphenylphosphine abstracts a bromine atom from **119**, which forms a phosphorous ylide (**120**). The carbanion of the ylide nucleophilically attacks aldehyde **75**, which forms a betaine intermediate (**121**) that quickly closes to an oxaphosphatane intermediate (**122**). A 2+2 retro cycloaddition extrudes triphenylphosphine oxide to afford the product dibromoolefin **76**.

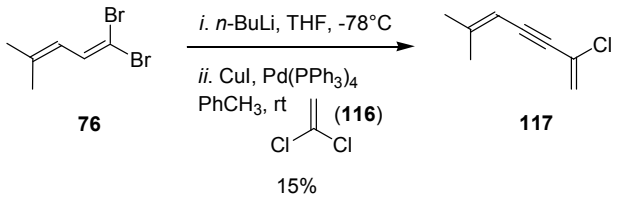
Scheme 30. Mechanism of Corey-Fuchs Olefination.



Our next aim was to convert dibromoolefin **76** to a terminal alkyne, using *n*-butyllithium followed by an aqueous ammonium chloride quench. No alkyne was isolated, so we suspected that it was volatile. We therefore tested whether the elimination was working by conducting another elimination using trimethylsilyl chloride to quench the alkynyllithium, to make the less volatile TMS-protected acetylene. The product was isolated in high yield.

In light of these results, we decided to convert dibromoolefin **76** directly to chloroynediene **117** without synthesizing the alkyne in a separate step, via a one-pot elimination-Sonogashira reaction (Scheme 31). A Sonogashira coupling of a terminal alkyne and vinylidene dichloride has been precedented[175], however, one in which the alkynyllithium is used has not and would therefore comprise a novel transformation.

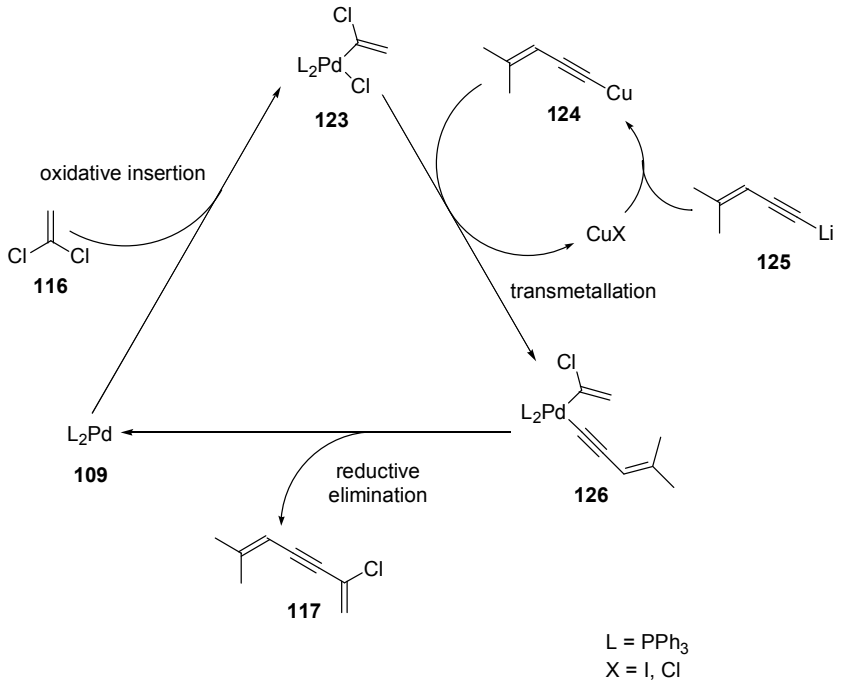
Scheme 31. Synthesis of Chloroynediene **117** via *In Situ* Elimination-Sonogashira. Coupling.



Slightly over 2 equivalents of *n*-Butyllithium were added dropwise to a solution of **76** in THF at –78°C. After 2 hours of stirring at –78°C, a separate flask was charged with tetrakis(triphenylphosphine) palladium(0), toluene, and vinylidene dichloride, and the first flask containing the intermediate alkynyllithium was cannulated to this second flask. Copper (I) iodide was added, and the reaction was stirred overnight. After chromatography with *n*-pentane, chloroynediene **117** was afforded in 15% yield. Most other attempts at this synthesis either failed or resulted in extremely low yields. Instability and/or volatility of **117** was strongly suspected.

The mechanism of this Sonogashira coupling[174] (Scheme 32) uses the alkynyllithium (**125**) generated from the *n*-BuLi promoted elimination of the dibromoolefin directly, instead of a terminal alkyne and amine base.

Scheme 32. Mechanism of the Sonogashira Cross-Coupling.



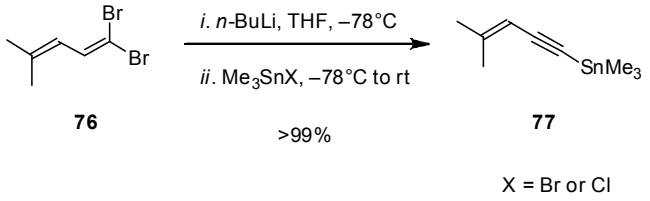
Bis(triphenylphosphine) palladium(0) (**109**) undergoes an oxidative insertion into one of the carbon-chloride bonds of vinylidene dichloride **116** to form palladium(II) complex **123**. Alkynylcuprate **124**, generated from the transmetallation of copper (I) iodide with alkynyllithium **125**, transmetallates with palladium to form alkynylpalladium complex **126**. Complex **126** then undergoes reductive elimination to form chloroynediene **117**, while regenerating the catalyst.

3.2.1.2 Via Stille Cross-Coupling

Our other approach towards the synthesis of the chloroynediene appendage was through a Stille cross-coupling of an alkynylstannane with vinylidene dichloride. This synthesis uses the same intermediate dibromoolefin **76** as in the elimination-Sonogashira approach.

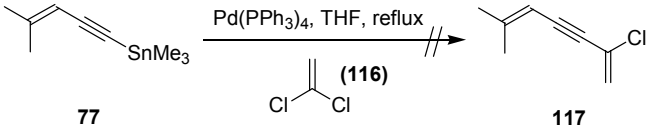
Treatment of **76** with *n*-butyllithium in THF at –78°C, followed by quenching with trimethyltin bromide or trimethyltin chloride and warming to room temperature afforded alkynylstannane **77**[150] in high purity (Scheme 33).

Scheme 33. Synthesis of Alkynylstannane **77**.



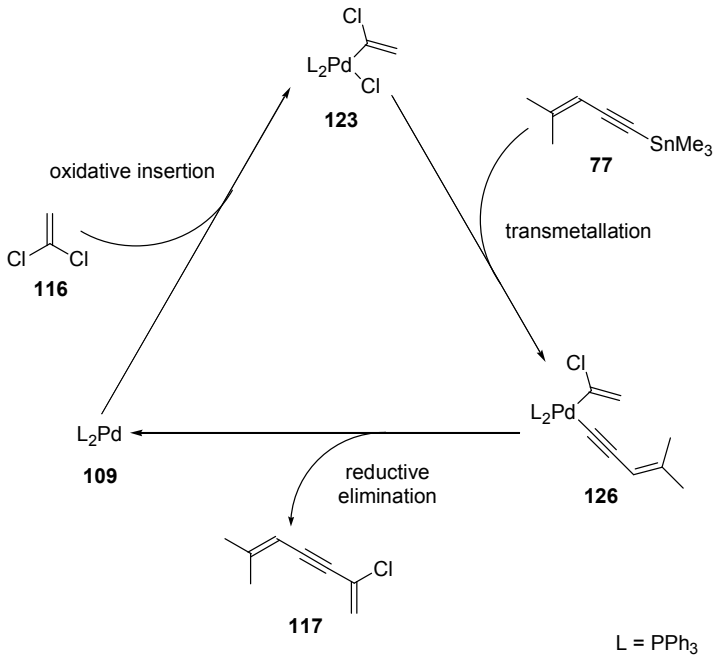
Although Parrain[150] purified this stannane by distillation, we found that subsequent chromatography decomposed the product. Stannane **77** must also be used within 2-3 days to avoid decomposition. The stannane was thus taken without purification into the following Stille coupling step (Scheme 34).

Scheme 34. Synthesis of Chloroynediene **117** via Stille Cross-Coupling.



Stannane **77** was added to a mixture of tetrakis(triphenylphosphine) palladium (0) and vinylidene dichloride in THF and refluxed overnight. The catalytic cycle of this Stille cross-coupling[174] is similar to that of the Sonogashira coupling, and shares some of the same steps (Scheme 35).

Scheme 35. Mechanism of the Stille Cross-Coupling.



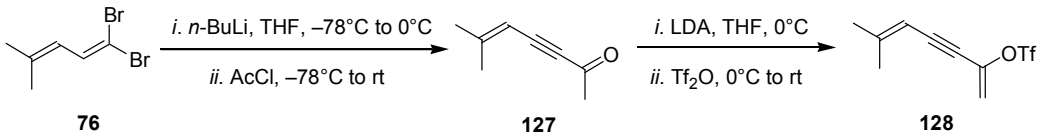
Bis(triphenylphosphine) palladium(0) (**109**) oxidatively inserts into a carbon-chlorine bond of vinylidene dichloride **116** to form palladium(II) complex **123**. Transmetallation of alkynylstannane **77** with complex **123** yields alkynylpalladium complex **126**. Reductive elimination generates chloroynediene **117** and regenerates the catalyst.

The reaction generated no product, and all of stannane **77** and vinylidene dichloride **116** were consumed.

3.2.2 Triflylynediene Coupling Partner 128

As a result of our difficulties in synthesizing the chloroynediene, the synthesis of a triflate instead of a chloride as the coupling partner with the stannylfuranone was investigated. We originally perceived that the triflate would be more stable and less volatile than the chloroynediene, and would also give a higher yield in the Stille coupling with the stannylfuranone. The synthesis[176] starts from dibromoolefin **76**, and is shown in Scheme 36.

Scheme 36. Synthetic Route Toward Triflylynediene **128**.

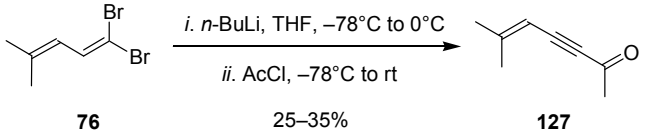


Elimination of dibromoolefin **76** with *n*-butyllithium will yield the alkynyllithium, which can be quenched with acetyl chloride to yield alkynyl methyl ketone **127**, also known as taxifolione. Taxifolione is a member of the Caulerpenyne family of natural products, and is of biogenetic significance[146]. Conversion of taxifolione into its corresponding enol triflate using a strong base and trifluoromethanesulfonic anhydride will yield triflylynediene **128**.

3.2.2.1 Synthesis of Taxifolione (127)

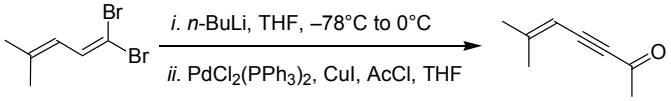
Our initial efforts at synthesizing **128** using the aforementioned treatment of an alkylnyllithium with acetyl chloride (Scheme 37) resulted in unacceptable yields in the range of 25–35%. The product was only able to be semi-purified via column chromatography.

Scheme 37. Acyl Substitution of Acetyl Chloride with Alkynyllithium to Synthesize **127**.



We then focused our attention on using palladium-catalyzed methods to construct the ketone. Our first approach was an *in situ* elimination-Sonogashira coupling (Scheme 38) analogous to that used in our first attempt to synthesize **117** (Section 3.2.1.1). The mechanism is the same as that shown in Scheme 32.

Scheme 38. *In Situ* Elimination-Sonogashira Coupling to Synthesize **127**.

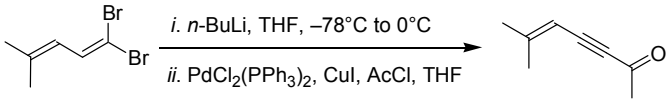


76 40% **127**

The isolated yield was 40%, a modest improvement over our initial efforts.

We then tested the efficacy of a Negishi cross-coupling[177] in assembling the two fragments (Scheme 39).

Scheme 39. Negishii Coupling to Synthesize **127**.

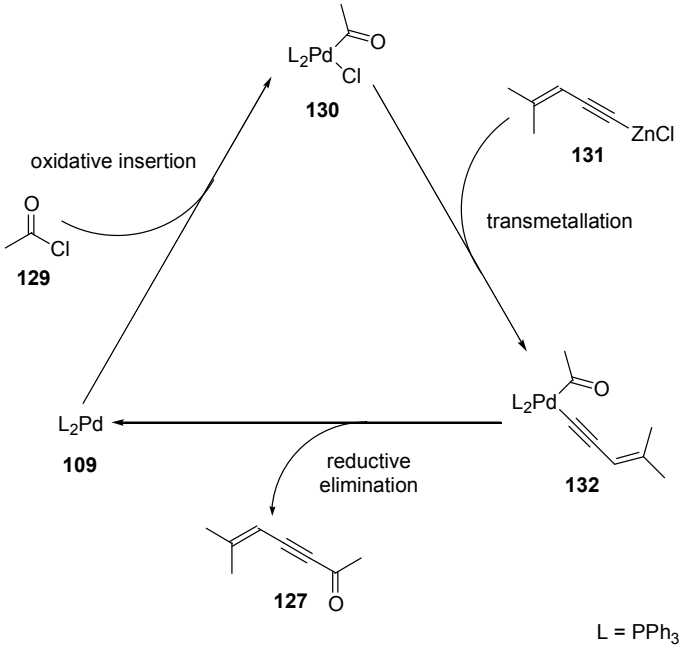


76 40% **127**

After elimination and lithium-halogen exchange with *n*-butyllithium at –78°C, we treated the alkynyllithium with purified zinc chloride at –10°C to generate the alkynylzinc chloride. This solution was added slowly to a mixture of tetrakis(triphenylphosphine) palladium (0) and acetyl chloride in tetrahydrofuran at –10°C.

The mechanism of this Negishi cross-coupling is shown in Scheme 40[174].

Scheme 40. Mechanism of the Negishi Cross-Coupling.

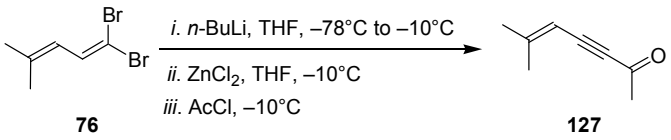


Bis(triphenylphosphine) palladium(0) (**109**) oxidatively inserts into the carbon-chlorine bond of acetyl chloride **129** to form palladium(II) complex **130**. Transmetallation of alkynylzinc chloride **131** with complex **130** yields alkynylpalladium complex **132**. Reductive elimination generates taxifolione (**127**) and regenerates the catalyst.

The isolated yield of the reaction was 23%. Despite this, the Negishii coupling of an acid chloride with an alkynylzinc chloride[178] is not extensively precedented, and is therefore novel.

We next decided to perform a nucleophilic acyl substitution using an alkynylzinc chloride instead of an alkynyllithium, under the assumption that possible bis addition of the alkynyl group would be less likely due to the lower nucleophilicity of alkynylzinc chlorides (Scheme 41).

Scheme 41. Synthesis of **127** via Acyl Substitution of Acetyl Chloride with an Alkynylzinc Chloride.



76 **127**

54%

Dibromoolefin **76** was lithium-bromide exchanged with *n*-butyllithium at –78°C, then warmed to –10°C to effect elimination and make the corresponding alkynyllithium. A solution of unpurified zinc chloride in THF was added slowly at –10°C to generate the alkynylzinc chloride. After warming to –10°C, acetyl chloride was added dropwise. The reaction proceeded in 54% isolated yield, a marked improvement over previous efforts.

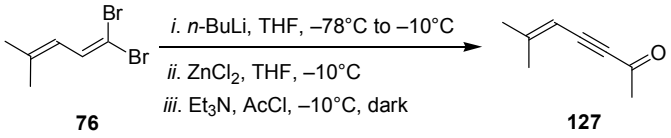
Initial attempts to optimize this approach gave unexpected results. We tested the same conditions, using purified and dried zinc chloride, and observed a surprisingly low 40% yield. We then made an attempt to reduce possible bis addition of the alkynyl group by varying the order of addition of reagents, by adding the freshly prepared alkynylzinc chloride solution dropwise to an excess of acetyl chloride in THF. A disappointing 42% yield was obtained.

We then decided to perform a different variation of the original set of conditions shown in Scheme 41. The revised procedure was operationally identical to those conditions up until generation of the alkynylzinc chloride, at which point the solution was cooled back down to –78°C, and 4 equivalents of acetyl chloride were added quickly. The solution was then warmed to –10°C. The objective of this procedure was to add a large excess of acetyl chloride at a temperature at which no reaction could occur, to allow homogeneous mixing of the electrophile in the solution before warming it to a temperature at which the nucleophile can attack it. We envisioned that this may be a more effective method of reducing bis addition than our original strategy of adding the alkynylzinc chloride to an excess of acetyl chloride. A yield of 61% was observed, the best achieved thus far.

This is a significant result in that there are no examples of an elimination of a gem-dibromoolefin to give an alkynylmetal species, which is then used in a nucleophilic acyl substitution with an acid chloride *in situ* to generate an alkynyl ketone. There is, however, one example in which the alkyne is isolated, then used in a separate subsequent nucleophilic substitution with an acid chloride[179].

We made a final attempt at increasing the yield of the taxifolione synthesis by forming the ketene of acetyl chloride to undergo nucleophilic attack by the alkynylmetal species *in situ* (Scheme 42).

Scheme 42. Synthesis of **127** via Ketene Trapping of an Alkynylzinc Chloride.

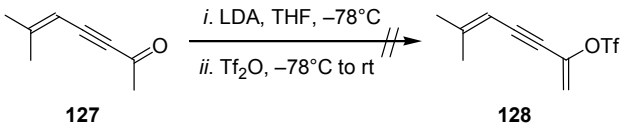


Dibromoolefin **76** was lithium-bromide exchanged with *n*-butyllithium at –78°C, then warmed to –10°C to effect elimination and generate the corresponding alkynyllithium. A solution of zinc chloride in THF was added slowly at –10°C to make the alkynylzinc chloride. After warming to –10°C, triethylamine was added slowly. The reaction was then continued in the dark, while acetyl chloride was added dropwise. After several hours, the reaction had become a viscous red material which was insoluble in the reaction solvent. Thin layer chromatography indicated the absence of taxifolione **127** or dibromoolefin **76**. We assumed that polymerization had occurred.

3.2.2.2 Synthesis of Triflylynediene 128

In our preliminary efforts towards the synthesis of triflylynediene **128** we used classical conditions for conversion of a ketone to an enol triflate (Scheme 43).

Scheme 43. Synthesis of Triflylynediene **128** via Enolate Trapping.

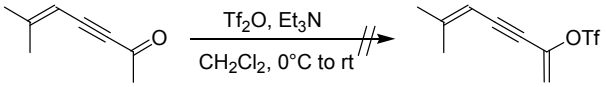


Taxifolione (**127**) was converted to its lithium enolate using lithium diisopropylamide in THF at –78°C. The enolate was quenched with undistilled trifluoromethanesulfonic anhydride at –78°C and the reaction warmed to room temperature. Only starting material **127** and a few side products were observed upon reaction.

We tested multiple other variations of the same conditions, substituting lithium hexamethyldisilazide, sodium hexamethyldisilazide, and sodium hydride as the base, and interchanging trifluoromethane sulfonic anhydride and *N*,*N*-bis(trifluoromethylsulfonyl)aniline as the triflating reagents. In all cases, mostly starting material and a few minor unidentified side products resulted.

We also tried adding trifluoromethane sulfonic anhydride to the ketone, followed by triethylamine to effect a "soft" enolization (Scheme 44).

Scheme 44. Synthesis of Triflylynediene **128** via Soft Enolization.

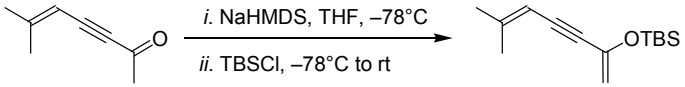


127 **128**

We found that the main component of the product mixture was the starting material, accompanied by some of the same unidentified minor products we observed in the enolate trapping experiments.

In light of our initial lack of success, we sought to determine whether the enolization of ketone **127** was the problem. We formed the enolate using sodium hexamethyldisilazide in tetrahydrofuran at –78°C, and quenched it with an excess of *tert*-butyl dimethylsilyl chloride (Scheme 45).

Scheme 45. Synthesis of Enol Silane **133**.

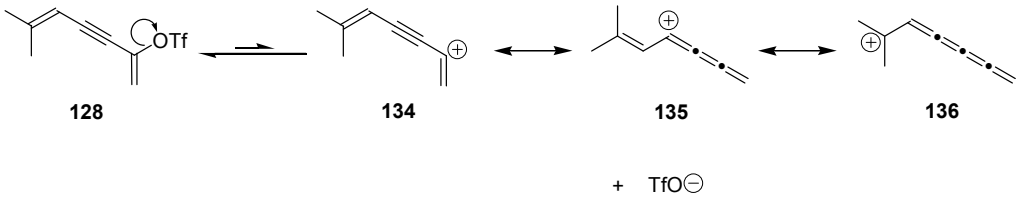


127 **133**

The product mixture contained pure enol silane **133** and the excess *tert*-butyl dimethylsilyl chloride. This confirmed that the enolization was not the problem, and that either the triflation was not working, or that the product triflate was unstable.

It is known that conjugated enol triflates are prone to heterolysis to give resonance-stabilized vinyl cations[180-184]. Since the vinyl cation of **128** is stabilized by three resonance contributors (**134**, **135**, **136**; Scheme 46), we suspected that our triflate is possibly undergoing S_N1 solvolysis with water during thin layer chromatography and workup to regenerate taxifolione, or that other decomposition pathways may be occurring via this intermediate.

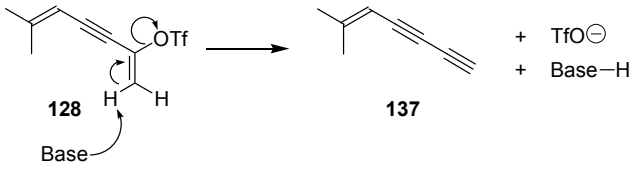
Scheme 46. Heterolysis of Triflylynediene **128** to Form a Vinyl Cation.



128 **134** **135** **136**

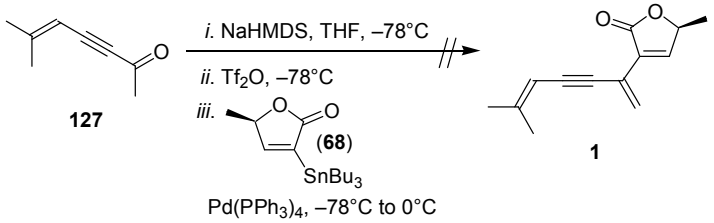
Triflate **128** could also undergo possible E2 elimination in the presence of excess base from the enolization step to generate the diyne (Scheme 47). This may be particularly facile as the hydrogen atom to be abstracted is conformationally locked *anti*- to the leaving group. The elimination can also occur via an E1 pathway on the vinyl cation **134** depicted in Scheme 46.

Scheme 47. E2 Elimination of Triflate **128** to Form a Diyne.



We observed during the enolate trapping experiments that when the triflating reagent was added to the enolate at –78°C, the color of the reaction turned from yellow to a deeper yellow. When this mixture was warmed to room temperature, the color turned brown or black. This led us to believe in the possibility that the triflate was successfully synthesized, but decomposed back to starting material and minor products when warmed to room temperature. Based on this assumption, we attempted to synthesize Trocheliophorolide A in one pot by generating triflylynediene **128** at –78°C, then adding catalytic tetrakis(triphenylphosphine) palladium(0) and stannane **68** to perform the Stille coupling *in situ* (Scheme 48).

Scheme 48. Attempted *In Situ* Enolization–Triflation–Stille Coupling to Form Trocheliophorolide A.

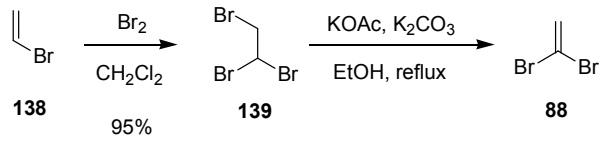


Although all of taxifolione **127** and stannane **68** were consumed, no product was formed by ^{1}H NMR.

3.2.3 Synthesis of Vinylidene Dibromide (88)

Due to our difficulties in synthesizing an ynediene side chain coupling partner, we revised our approach to Stille couple vinylidene dibromide with stannylfuranone **68**, then use the resulting alkenyl bromide to cross-couple with an enynylmetal species to form the target natural product. Scheme 49 shows our initial attempt to synthesize vinylidene dibromide[185] (**88**).

Scheme 49. Synthesis of Vinylidene Dibromide **88**.



138 **139** **88**

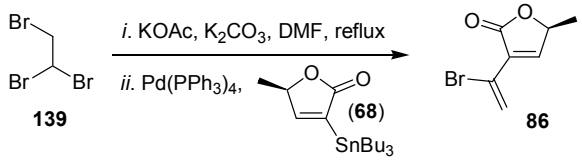
The first step in the synthesis is an electrophilic bromination of vinyl bromide **138**, which proceeded in 95% yield to give 1,1,2-tribromoethane **139**. The second step, a potassium acetate/potassium carbonate–promoted elimination of hydrogen bromide[185], is under investigation.

3.3 Final Convergence to Synthesize Trocheliophorolide A

3.3.1 Synthesis of Alkenyl Bromide 86

According to the literature, vinylidene dibromide **88** is unstable and difficult to isolate, As such, we plan on performing the Stille coupling *in situ* immediately after generating it. Because our previous attempts at synthesizing an ynediene side chain substituted with a triflyl or halo group did not work, we will avoid performing the Stille coupling with the enynylmetal species generated from gem-dibromoolefin **76** and instead attempt to couple vinylidene dibromide **88** with stannylfuranone **68** in the hope that the resulting alkenyl bromide will be stable and isolable (Scheme 50).

Scheme 50. Stille Coupling of *In Situ* Generated Vinylidene Dibromide with Stannylfuranone **68**.



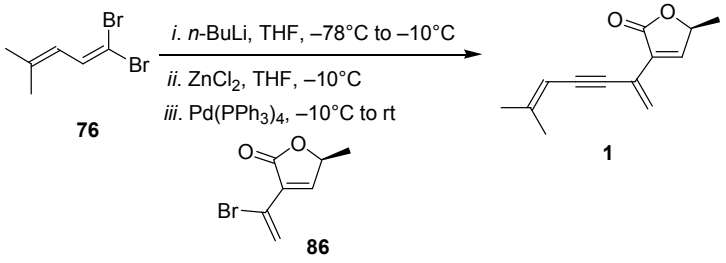
139 **86**

1,1,2-tribromoethane (**139**) will be eliminated using potassium carbonate as the base under reflux in *N,N*-dimethylformamide. The resulting *in situ* generated vinylidene dibromide (**88**) will be subjected to an addition of catalytic tetrakis(triphenylphosphine) palladium (0) and stannylfuranone **68** to afford alkenyl bromide **86**.

3.3.2 Synthesis of Trocheliophorolide A

The final step of the synthesis is a palladium-catalyzed cross-coupling of alkenyl bromide **86** with the alkynylzinc chloride species generated from gem-dibromoolefin **76** (Scheme 51).

Scheme 51. Negishi Coupling to Synthesize Trocheliophorolide A (**1**).



Other alkynylmetal species that may be tested include alkynylstannanes (Stille coupling) and alkynylcuprates (Sonogashira coupling).

4.0 Conclusions

In summary, an efficient synthetic approach to Trocheliophorolide A has been explored. Our studies have accomplished the following:

1. An improved synthesis of stannylfuranone **68**, a versatile Stille coupling partner which can be used in the construction of a large array of *(S)-β*-angelica lactone natural products, through the intermediacy of the less volatile and more stable tosylate intermediate **87** and use of the palladium-catalyzed hydrostannation;
2. Efficient application of the chiral pool approach to incorporate the stereocenter of the lactone ring;
3. The highest-yielding published synthesis[186] of the natural product taxifolione (**127**).
4. Established that the chloroynediene (**117**) and triflylynediene (**128**) coupling partners are likely not suitable for cross-coupling due to their difficulty of synthesis and probable instability;
5. Initiation of the synthesis of alkenyl bromide **86**, a potentially more stable coupling partner than the chloroynediene (**117**) and triflylynediene (**128**).
6. Significant progress toward the total synthesis of Trocheliophorolide A (**1**), the completion of which will be the first synthesis of a member of a new class of bioactive *(S)-β*-angelica lactone natural products with an ynediene side chain;

Part II: Studies on the Development of a Palladium-Catalyzed Carbonylative Cross-Coupling Towards the Synthesis of Alkenyl Alkynyl Ketones.

1.0 Introduction and Background

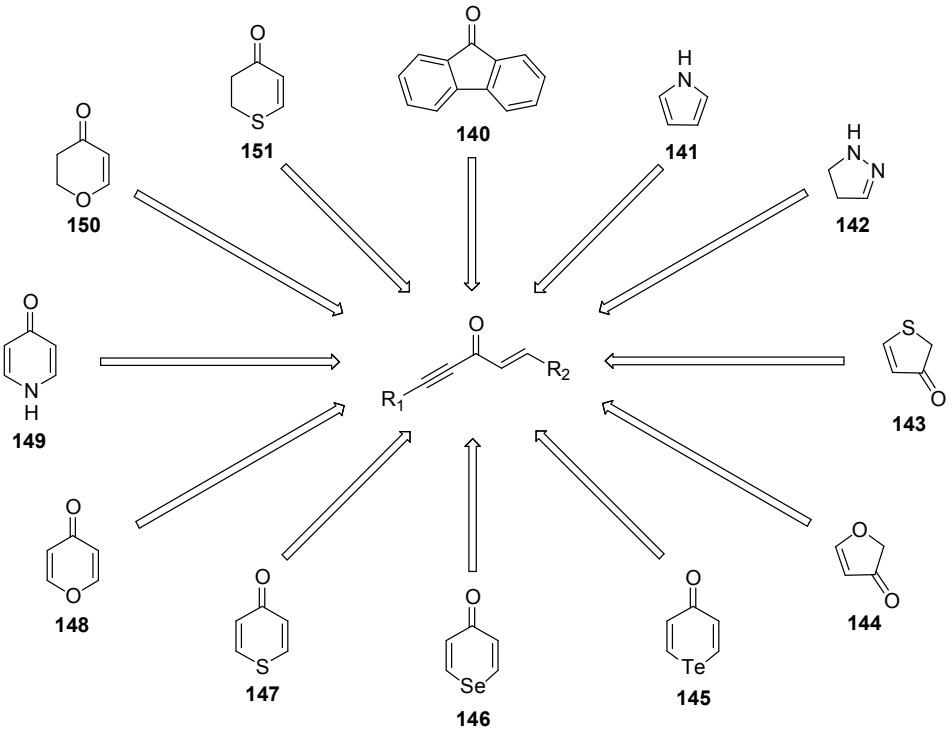
1.1 Synthetic Utility of Alkenyl Alkynyl Ketones

The alkenyl alkynyl ketone structural unit is widely used as a versatile component of synthetic intermediates and precursors, and is found in a number of bioactive natural products. As such, our goal is to develop a more mild and efficient synthesis towards this important functionality.

1.1.1 Synthesis of Heterocycles Using Alkenyl Alkynyl Ketones

A large number of variably substituted heterocycles have been synthesized from alkenyl alkynyl ketones in the last 50 years, including fluorenones (**140**)[187], pyrroles (**141**)[188], 4,5-dihydropyrazoles (**142**)[189], thiophen-3-one (**143**)[190], furan-3-one (**144**)[191,192], telluropyran-4-ones (**145**)[193-196], selenopyran-4-ones (**146**)[194-196], thiopyran-4-ones (**147**)[194-196], pyran-4-ones (**148**)[194-197], 1*H*-Pyridin-4-one (**149**)[190], 2,3-dihydropyran-4-one (**150**)[198], and 2,3-dihydrothiopyran-4-one (**151**)[199,200] (Figure 4).

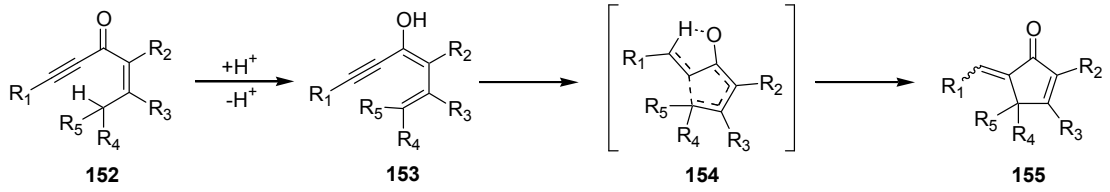
Figure 4. Heterocycles Accessible From Alkenyl Alkynyl Ketones.



1.1.2 Synthesis of Carbocycles Using Alkenyl Alkynyl Ketones

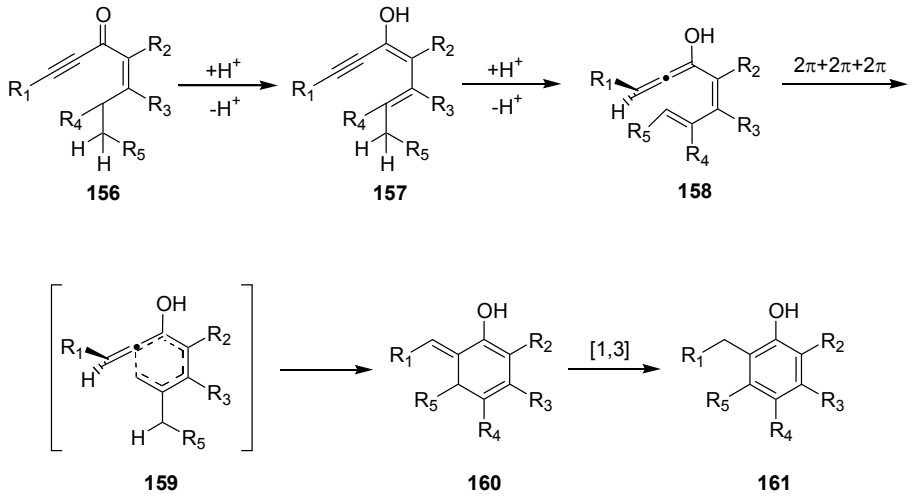
A substantial amount of research investigating the acid-catalyzed electrocyclization of alkenyl alkynyl ketones to form methylenecyclopentenones[201-209] has been performed, and applied to the synthesis of several natural products[201-204,207-209]. Scheme 52 shows the mechanism of this reaction. Variably substituted propenyl alkynyl ketone **152** undergoes acid-catalyzed tautomerisation to conjugated enol **153**, which then undergoes the electrocyclization to give methylenecyclopentenone **155**.

Scheme 52. Electrocyclization of Alkenyl Alkynyl Ketones to Methylenecyclopentenones.



An alternate pathway (Scheme 53) allows the synthesis of phenol derivatives[207,208,210]. Variably substituted butenyl alkynyl ketone **156** undergoes acid-catalyzed enolization to **157**, which undergoes a tautomerisation to allene **158**. A 2+2+2 electrocyclization affords exocyclic olefin **160**, which isomerizes to phenol **161**.

Scheme 53. Electrocyclization of Alkenyl Alkynyl Ketones to Phenol Derivatives.

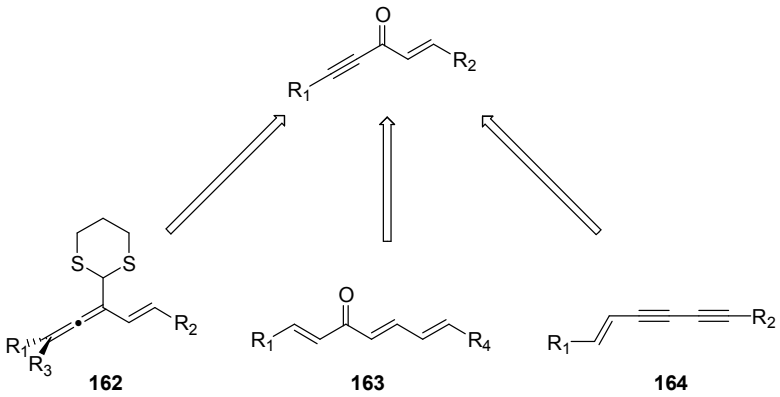


Phenols can also be synthesized from alkenyl alkynyl ketones via ring-closing metathesis[211].

1.1.3 Synthesis of Acyclic Structures Using Alkenyl Alkynyl Ketones

There have been several acyclic structures synthesized from alkenyl alkynyl ketones, including vinyl allenes (**162**)[212], 1,4,6-trien-3-ones (**163**)[213], and 1-ene-3,5-diynes (**164**)[214] (Figure 5).

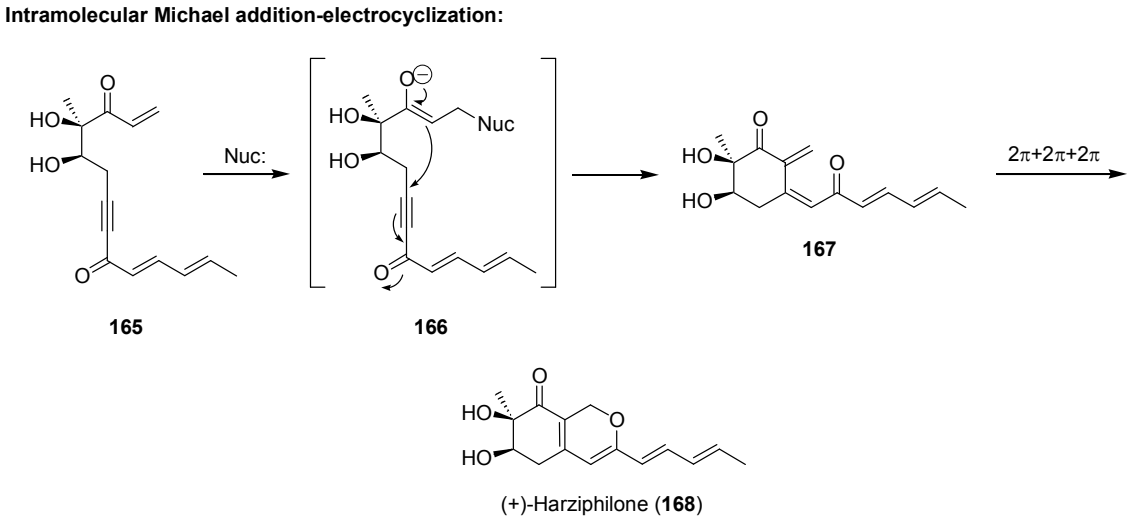
Figure 5. Acyclic Structures Accessible From Alkenyl Alkynyl Ketones.



1.1.4 Miscellaneous Synthetic Applications of Alkenyl Alkynyl Ketones

Alkenyl alkynyl ketones have been used as substrates in various other synthetic contexts, including electrocyclizations[215], Diels-Alder cycloadditions[216-219], palladium-catalyzed cycloadditions[220], and as Michael acceptors in silyl enol ether conjugate additions[221]. Scheme 54 shows an example of an intramolecular Michael addition followed by an electrocyclization to build the bicyclic ring system of (+)-Harziphilone (**168**)[215], and the Michael addition of a silyl enol ether to an alkenyl alkynyl ketone to afford δ-keto silyl enol ether (**171**)[221].

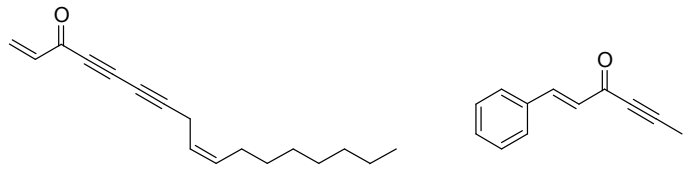
Scheme 54. Electrocyclization and Michael addition of Alkenyl Alkynyl Ketones.



1.1.5 Alkenyl Alkynyl Ketones as Structural Units in Natural Products and as Intermediates Towards their Synthesis

Many natural products containing the alkenyl alkynyl ketone structural feature have been isolated from natural sources. The polyacetylenic Panax family of natural products[222-259] comprise the majority of them, and their members feature cytotoxic[260], anti-inflammatory[230,261,262], antimycotic[263,264], antileukemic[265,266], anticarcinomic[267], and ACAT inhibitory[268] agents. Chalconic natural products include nematocides[269], fungicides[269-271], antimicrobial agents[272], antiplatelet aggregation agents[273,274], and anti-inflammatory agents[273,274]. Figure 6 shows an example of a member of the Panax family of natural products, falcarinone (**172**)[263], and a chalconic natural product, Capillaridin C (**173**)[273,274].

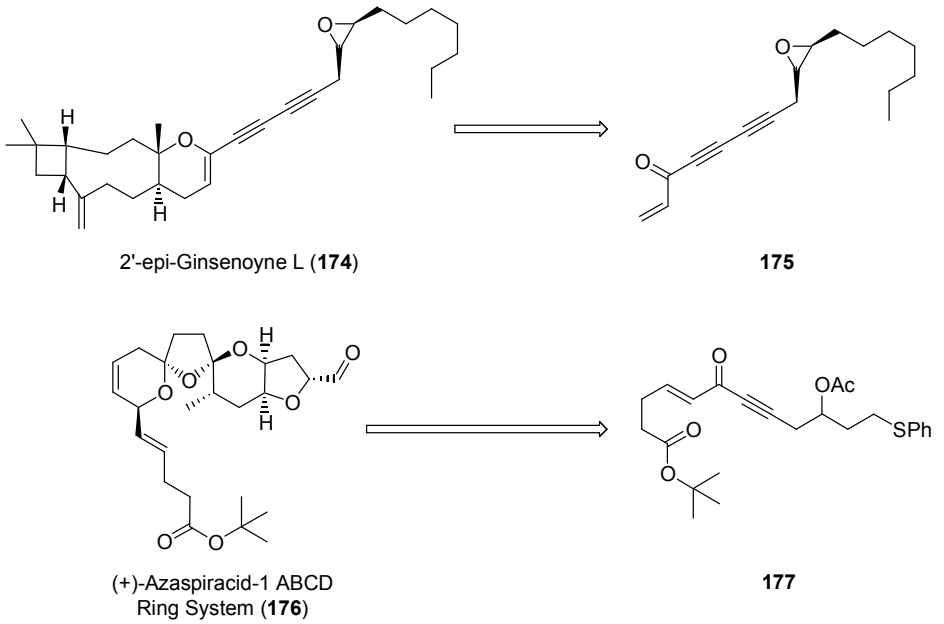
Figure 6. Falcarinone (**172**) and Capillaridin C (**173**).



Falcarinone (**172**) Capillaridin C (**173**)

In addition to their presence in natural products, alkenyl alkynyl ketones have been used as intermediates in the synthesis of many natural products, including (+)-Bisorbibutenolide[275], (+)-Bisorbicillinolide[275], (+)-Bisorbicillinol[275], Bullatenone[198], 2'-epi-Ginsenoyne L[276], Griseofulvin[277], (+)-Harziphilone[215], Juncusol[202], Methylenomycin A[203], Methylenomycin B[209], Panaxytriol[278], Petrofuran[279], Xanthocidin[203], as well as in AB Taxane ring systems[216,218,219], the ABCD ring fragment of (+)-Azaspiracid-1[280], the C1-C13 domain of Discodermolide[281], the Phomactin core[282], and the Spirastrellolide A dioxatrispiroketal[283]. Figure 7 shows the alkenyl alkynyl ketone intermediates used en route to 2'-epi-Ginsenoyne L (**174**)[276] and to the ABCD ring system of (+)-Azaspiracid-1 (**176**)[280].

Figure 7. Intermediates in the Syntheses of 2'-epi-Ginsenoyne L (**174**) and the ABCD Ring System of (+)-Azaspiracid-1 (**176**).



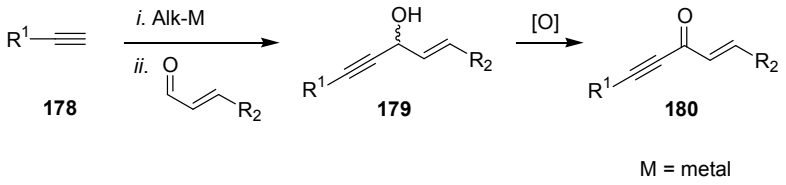
1.2 Existing Methods of Alkenyl Alkynyl Ketone Synthesis

An array of synthetic methods are used to synthesize alkenyl alkynyl ketones; however, most of them have significant limitations in scope or require multiple steps.

1.2.1 Synthesis of Alkenyl Alkynyl Ketones via Oxidation of an Alkenyl Alkynyl Carbinol

The most widely used method to make alkenyl alkynyl ketones is via the oxidation of a secondary carbinol to which an alkenyl and an alkynyl group are attached[188,199,268,276,284-296]. The alcohol is most often generated by the trapping of an alkynylmetal (usually an alkynyllithium) with an α,β-unsaturated aldehyde. The general form of this sequence is shown in Scheme 55.

Scheme 55. Alkynylmetal Trapping and Oxidation.

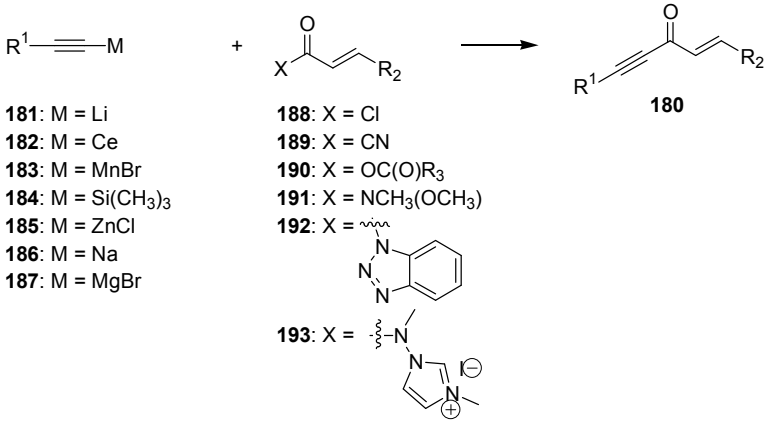


The primary drawbacks of this method are that the trapping step is often low-yielding; the synthesis requires three steps (two of them in one pot); and the alkyne is often treated with a strong base to generate the alkynylmetal, which may pose chemoselectivity problems in the presence of other base-sensitive functionalities.

1.2.2 Synthesis of Alkenyl Alkynyl Ketones via Nucleophilic Acyl Substitution

Another frequently used method employs the nucleophilic acyl substitution by an alkynylmetal of an acid chloride or acid chloride synthetic equivalent. There are examples of alkynyllithium (**181**)[297], alkynylcerium (**182**)[272], alkynylmanganese bromide (**183**)[298], alkynyltrimethylsilane (**184**)[214,299], and alkynylzinc chloride (**185**)[300] additions to acid chlorides (**188**). Other examples include alkynyltrimethylsilane (**184**) additions to acyl cyanides (**189**)[301], alkynylsodium (**186**) additions to acid anhydrides (**190**)[302], alkynyllithium (**181**) additions to weinreb amides (**191**)[280], alkynylmagnesium bromide (**187**) additions to *N*-acylbenzotriazoles (**192**)[303], and alkynyllithium (**181**) additions to 1-(*N*-acyl-*N*-methylamino) imidazolium iodides (**193**)[304] (Scheme 56).

Scheme 56. Alkenyl Alkynyl Ketone Synthesis via Nucleophilic Acyl Substitution.

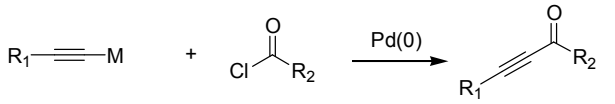


The primary problem with this method is the need to prepare the alkynylmetal species, the acid chlorides, and the acid chloride synthetic equivalents in separate syntheses, some requiring multiple steps. Additionally, the reactivity of several of the alkynylmetal species and of acid chlorides lends to incompatibility with a wide range of functionalities and a short shelf-life.

1.2.3 Synthesis of Alkenyl Alkynyl Ketones via Palladium-Catalyzed Cross-Coupling of an Alkynylmetal with an α,β-Unsaturated Acid Chloride

An approach that was pursued shortly following the advent of metal-catalyzed cross coupling chemistry is the palladium-catalyzed coupling of alkynylmetals with α,β-unsaturated acid chlorides. Alkynylalanes (**194**)[305], alkynylzinc chlorides (**195**)[178], and alkynylstannanes (**196**)[306] have all been coupled with acid chlorides (**197**) (Scheme 57).

Scheme 57. Palladium-Catalyzed Cross-Coupling of Alkynylmetals with Acid Chlorides.



194: M = $AlEt_2$
195: M = ZnCl
196: M = $SnBu_3$

197

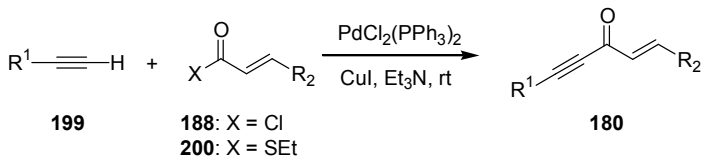
198

R_2 = alkenyl or phenyl

As previously discussed (Section 1.2.2), acid chlorides need to be synthesized separately, are highly reactive, and have a short shelf life. Furthermore, alanes can sometimes be so highly reactive that they can add to the product ketone, as well as other carbonyl groups or electrophilic centers in the product or starting material. Alkynylzinc halides must usually be prepared *in situ*, and therefore cannot be purified prior to use, while alkynylstannanes can be unstable to chromatographic purification.

A closely related approach is the Sonogashira coupling of terminal alkynes (**199**) with acid chlorides (**188**)[299,307-314] (Scheme 58). Thioesters (**200**) have also been used in place of acid chlorides[315].

Scheme 58. Sonogashira Coupling of Terminal Alkynes and Acid Chlorides or Thioesters.

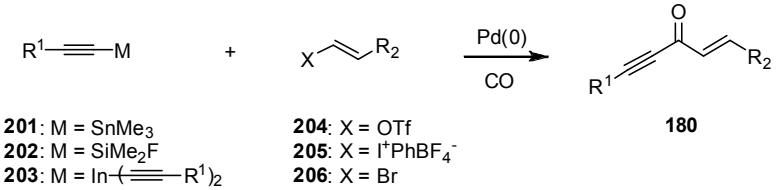


Although terminal alkynes are often more stable and easier to prepare, the same reactivity and shelf-life problem of the acid chloride coupling partner exists. In the case of thiol esters, the couplings are relatively low-yielding and thiol ester preparation is typically performed in a two-step synthesis from a carboxylic acid.

1.2.4 Synthesis of Alkenyl Alkynyl Ketones via Metal-Catalyzed Carbonylative Cross-Coupling

Another catalytic method for forming alkenyl alkynyl ketones employs carbon monoxide pressure to form the carbonyl functional group, instead of using an acylalkenyl cation synthon to incorporate it (Section 1.2.3). There are examples of carbonylative couplings between alkynylstannanes (**201**) and alkenyl triflates (**204**)[316,317] alkynylstannanes (**201**) and alkenyl phenyliodonium tetrafluoroborates (**205**)[318], alkynyldimethylfluorosilanes (**202**) and alkenyl phenyliodonium tetrafluoroborates (**205**)[319]; and trialkynylindiums (**203**) and alkenyl bromides (**206**)[320] (Scheme 59).

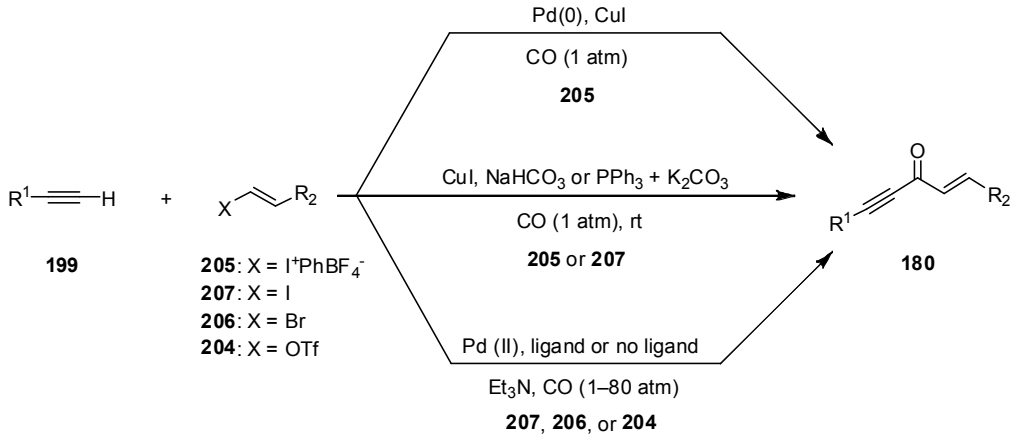
Scheme 59. Carbonylative Cross-Couplings of Alkynylmetals With Alkenyl Coupling Partners.



Carbonylative Sonogashira and Sonogashira-type couplings accomplish the same transformation using terminal alkynes, eliminating the need to separately synthesize an alkynylmetal species (Scheme 60). Palladium-catalyzed Sonogashira reactions of alkenyl

phenyliodonium tetrafluoroborates (**205**)[321], copper (I) iodide-catalyzed couplings of alkenyl phenyliodonium tetrafluoroborates (**205**)[321] or alkenyl iodides (**207**)[321,322], and palladium-catalyzed couplings of alkenyl halides (**207**, **206**)[323,324] or triflates (**204**)[325] without the need for a copper (I) cocatalyst are all known.

Scheme 60. Carbonylative Sonogashira and Sonogashira-Type Couplings.

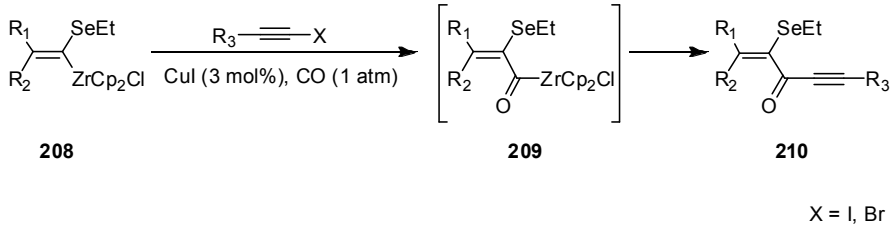


The drawback of the Sonogashira coupling approach is rooted in the alkenyl phenyliodonium tetrafluoroborate synthesis. These must be synthesized from the corresponding silane[326], which itself must be synthesized. Therefore, its preparation requires multiple steps. An additional drawback is that the iodosylbenzene that is used in its synthesis is unstable and potentially explosive[327-329].

In the case of the copper (I) catalyzed couplings, only a relatively small percentage of the tested coupling partners underwent the reaction, so it is very limited in scope. The palladium-only catalyzed coupling reactions have not been successful when electron deficient alkynes are employed (R_1 = CO_2Et, $CH(OEt)_2$), severely restricting this synthetic approach.

A particularly unusual carbonylative coupling approach is the copper (I) iodide-catalyzed cross-coupling of α-seleno alkenylzirconocenes with alkynyl halides under a carbon monoxide atmosphere (Scheme 61).

Scheme 61. Carbonylative Cross-Couplings of Alkynylmetals With Alkenyl Coupling Partners.

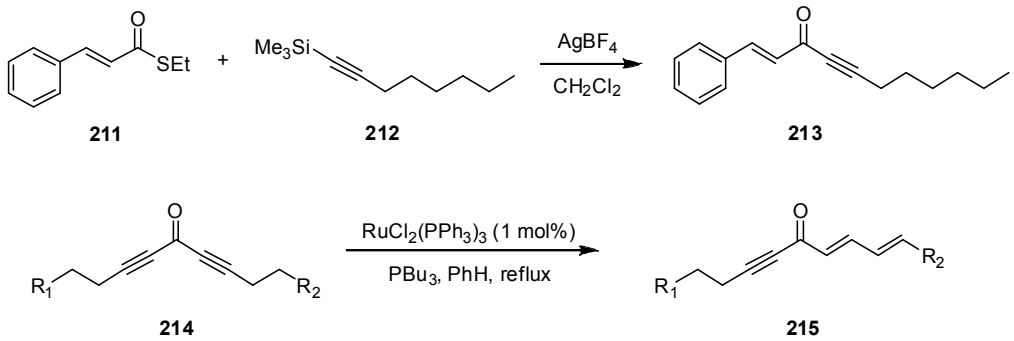


Although the reaction conditions are mild, preparation of the alkenyl zirconocene chloride is limited to hydrozirconation of alkynes at the least sterically hindered carbon[330]. In addition, hydrozirconation can occur with olefins and has been shown to open heterocyclic rings[331]. Therefore, efficient preparation of vinyl zirconocenes starting with internal alkynes is very difficult and the reagent must not be used when olefins and other sensitive functionalities exist elsewhere in the starting material. As a result this method is unsuitable as a general process because of this substrate limitation.

1.2.5 Miscellaneous Methods of Alkenyl Alkynyl Ketone Synthesis

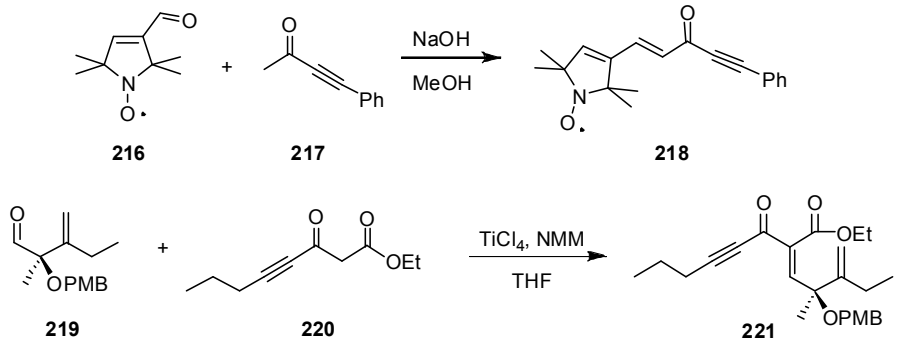
There are many other less general methods of synthesizing alkenyl alkynyl ketones. Catalytic methods include the silver (I) nitrate-catalyzed coupling of alkenylthioesters (**211**) with alkynyltrimethylsilanes (**212**)[332] and the ruthenium-catalyzed regioselective isomerization of one triple bond of a dialkynylketone (**214**) to generate an alkynyl dienyl ketone (**215**)[333,334] (Scheme 62).

Scheme 62. Miscellaneous Catalytic Methods to Synthesize Alkenyl Alkynyl Ketones.



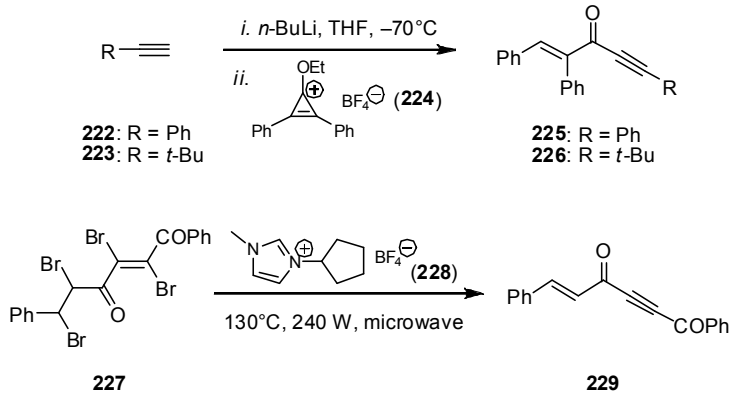
Scheme 63 shows the condensation reactions used to synthesize alkenyl alkynyl ketones. There has been an example of a 3-formyl pyrroline (**216**) undergoing an aldol condensation with an alkynyl methyl ketone (**217**)[335], as well as the use of a Knoevenagel condensation of an aldehyde (**219**) with a β-ketoester (**220**) in Deng's syntheses of Bisorbicillinolide, Bisorbicillinol, and Bisorbibutenolide[275].

Scheme 63. Miscellaneous Condensation Methods to Synthesize Alkenyl Alkynyl Ketones.



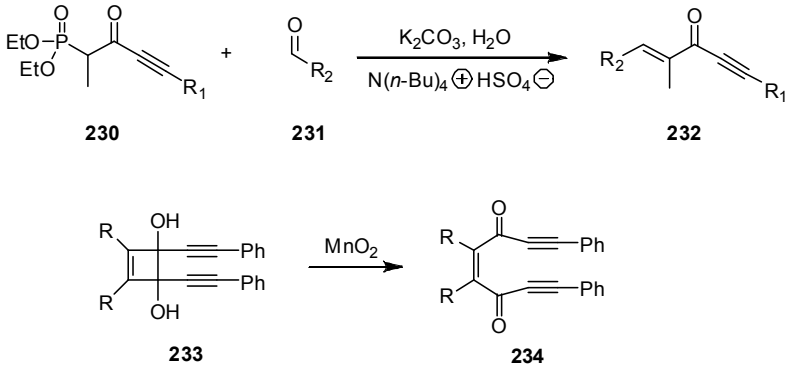
Scheme 64 shows some of the particularly unusual methods used to synthesize alkenyl alkynyl ketones. The first involves the ring opening of a 1-ethoxy-2,3-diphenyl cyclopropenylium salt (**224**) by an alkynyllithium species (**222**, **223**) to form the resultant ketone (**225**, **226**)[336]. The second example depicts the debromination of a tetrabromo ketone (**227**) in an ionic liquid (**228**) via microwave irradiation to afford the product ketone (**229**)[337].

Scheme 64. Miscellaneous Unusual Methods of Alkenyl Alkynyl Ketone Synthesis.



Some other methods include the Horner-Wadsworth-Emmons (HWE) olefination of a 2-oxo-3-alkynyl β-keto phosphonate ester (**230**)[338], and an oxidative ring opening of a cyclobut-3-ene-1,2-diol (**233**) to form the C_2-symmetrical diketone (**234**)[339,340] (Scheme 65).

Scheme 65. HWE Olefination and Oxidative Ring Cleavage Methods of Alkenyl Alkynyl Ketone Synthesis.

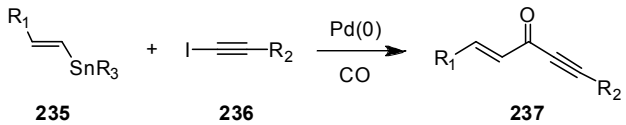


1.3 Our Proposed Methodology

1.3.1 Methodology Design

In light of the limitations of scope inherent in the existing methods, an alternate, more general approach towards alkenyl alkynyl ketones is under investigation. The method employs a palladium-catalyzed cross-coupling of alkenyl stannanes (**235**) with alkynyl iodides (**236**) under carbon monoxide pressure to form the resultant ketone (**237**, Scheme 66).

Scheme 66. Palladium-Catalyzed Carbonylative Coupling of Alkenyl Stannanes With Alkynyl Iodides.



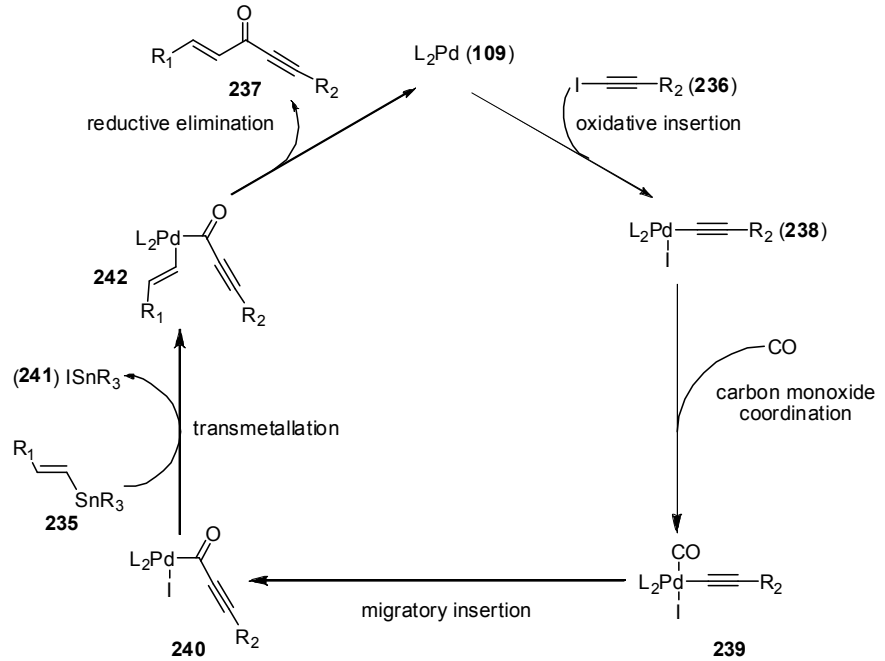
The benefits of this protocol are the following:

- Two carbon-carbon bonds formed in a single step.
- The reagents used are neutral and mild.
- Reagents are easily synthesized.
- The reagents are storable and have a long shelf-life.
- The alkynyl iodides and alkenyl stannanes are compatible with a broad range of sensitive functionalities.
- Alkynyl iodides with electron-withdrawing groups attached to the opposite end of the triple bond can be coupled.

1.3.2 Mechanism of Carbonylation

The proposed mechanism of the carbonylative cross-coupling is based on an analogy with existing carbonylative cross-coupling mechanisms[341] (Scheme 67).

Scheme 67. Catalytic Cycle of the Palladium-Catalyzed Carbonylative Cross-Coupling of Alkynyl Iodides With Alkenyl Stannanes.

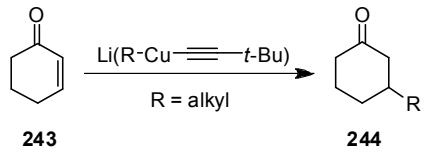


The first step of the catalytic cycle is the oxidative insertion of the palladium (0) complex (**109**) into the carbon-iodine bond of the alkynyl iodide (**236**) to form palladium (II) complex **238**. Carbon monoxide coordinates to the complex, which then undergoes migratory insertion to form acylpalladium complex **240**. The alkenyl group of stannane **235** transmetallates with palladium, generating acylalkenylpalladium complex **242** and a trialkyltin iodide (**241**). Reductive elimination yields the product ketone (**237**) while regenerating the catalyst (**109**).

1.3.3 Possible Problems

Alkynyl groups are used as dummy ligands in lithium diorganocuprate reagents for conjugate additions[342] since they transfer to the Michael acceptor at a lower rate than alkenyl or alkyl ligands[343] (Scheme 68).

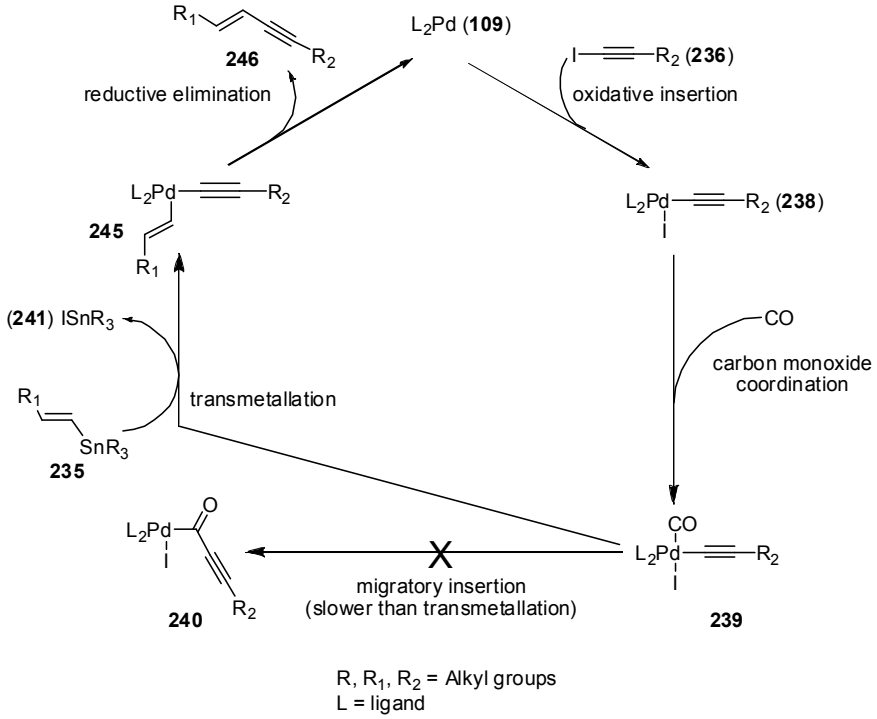
Scheme 68. Diorganocuprate Conjugate Addition Using Alkynyl Dummy Ligand.



243 **244**

As depicted in Scheme 69, by analogy it is possible that the alkynyl ligand of complex **239** migrates to carbon monoxide to form the acylalkynyl ligand of complex **240** more slowly than the transmetallation step occurs. If this happens, transmetallation will occur first, and the enyne (**246**) will likely be reductively eliminated, precluding formation of acylpalladium intermediate **240** and ultimately the desired ketone (**237**).

Scheme 69. Catalytic Cycle if Carbonyl Insertion is Rate-Limiting Step.



However, since the transmetallation step is rate-limiting in some palladium cross-coupling catalytic cycles, this step may occur more slowly than migratory insertion, allowing formation of **240** *before* transmetallation and therefore ultimately generating desired ketone **237**.

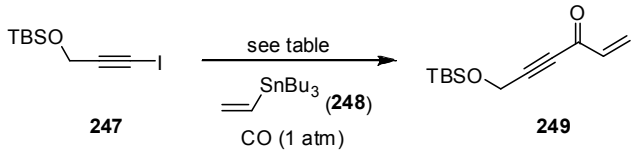
It has also been demonstrated that in cases where the non-carbonylated cross-coupled product is yielded, increasing the carbon monoxide pressure results in a higher yield of the carbonylation product[344].

2.0 Results and Discussion

2.1 Initial Carbonylation Attempts

Our first attempts were aimed at testing some common solvents and catalysts under 1 atm carbon monoxide pressure (Table 2). In all three test reactions, no desired product was yielded, and instead a complex mixture of products resulted. The analysis of entry 1 indicated that all of iodide **247** was consumed, while far less than an equimolar amount of stannane **248** reacted, the remainder recovered chromatographically. This led us to believe that possible side reaction(s) occurred that consumed the iodide faster than it could react via the desired pathway. In the case of entry 3, in which the stannane was the limiting reagent, both the stannane and the iodide were consumed. Since the iodide was in excess, it must have undergone side reactions in this case as well.

Table 2. Carbonylative Cross-Coupling of **247** and **248**.



247 **249**

Entry	**247** (equiv.)	**248** (equiv.)	**Catalyst**	**Solvent**	**Results**
1	1.0	1.1	$Pd(PPh_3)_4$	THF	— [a]
2	1.0	1.1	$PdCl_2(PPh_3)_2$	DMF	— [a]
3	1.2	1.0	$Pd_2(dba)_3$, PPh_3	THF	— [a]

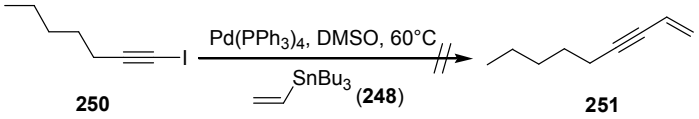
[a] No product isolated.

2.2 Direct Stille Cross-Coupling Optimization

In light of our lack of success in synthesizing and isolating ketone coupling product **249**, we focused our efforts on optimizing the direct Stille coupling reaction between the iodide and stannane to compartmentalize and therefore solve any problems that were occurring with the coupling reaction itself, before performing further carbonylation experiments. We also opted to synthesize and use 1-iodoheptyne to eliminate the possibility that the silyl ether was participating in or contributing to any side reactions.

In the first Stille coupling experiment, we used catalytic tetrakis(triphenylphosphine) palladium (0) and dimethylsulfoxide as the solvent, and heated the reaction at 60°C (Scheme 70). No product was detected in the reaction mixture.

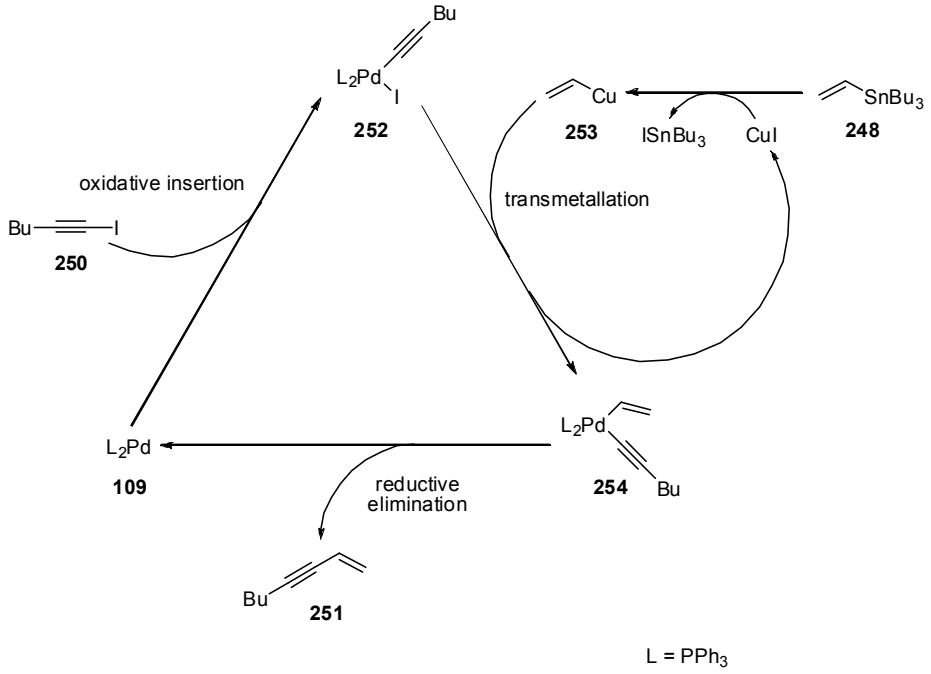
Scheme 70. Direct Cross-Coupling of **250** with **248**.



We then investigated conditions that were precedented in the literature for couplings of alkynyl iodides[345-357] and bromides[358-367] with alkenyl stannanes. The most common catalyst used is tetrakis(triphenylphosphine) palladium (0), while the most commonly used solvents are *N,N*-dimethylformamide and *N*-methylpyrrolidinone. In addition, the vast majority of couplings were performed using either cocatalytic copper (I) iodide[349,350,354,355,357,366,368,369], copper (I) chloride[361,365], or lithium chloride[351,356,362,370,371].

The function of copper (I) iodide[369] in the Stille cross-coupling is illustrated in Scheme 71.

Scheme 71. Mechanism of the Stille Cross-Coupling Cocatalyzed by Copper (I) Iodide.



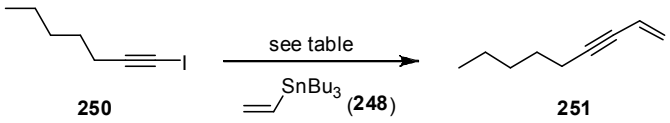
Copper (I) iodide transmetallates with the alkenylstannane (**248**), affording an alkenylcuprate (**253**) and tributyltin iodide. The alkenylcuprate (**253**) subsequently transmetallates with palladium complex **252** faster than the alkenylstannane, increasing the overall rate of reaction in cases in which transmetallation is the limiting step. The copper (I) iodide is regenerated to convert another molecule of alkenylstannane (**248**) to alkenylcuprate (**253**).

It has also been suggested that copper (I) iodide promotes dissociation of triphenylphosphine from palladium, raising the concentration of the 14-electron bis(triphenylphosphine) palladium (0) complex available for catalysis, and therefore providing another potential benefit of its use. This additional effect usually occurs in *N*-methylpyrrolidinone and to a lesser extent in *N,N*-dimethylformamide.

Copper (I) chloride performs essentially the same function as copper (I) iodide in Scheme 71, and lithium chloride is an additive sometimes used to suppress homocoupling of the alkynyl halide[372].

Table 3 shows our efforts in performing the direct coupling of iodide **250** and tributylvinyltin **248** using catalytic tetrakis(triphenylphosphine) palladium (0) in *N,N*-dimethylformamide.

Table 3. Direct Cross-Coupling of **250** and **248**.



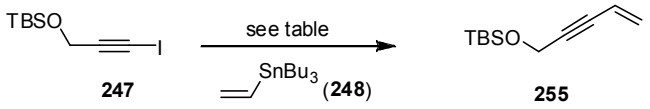
Entry	**250** (equiv.)	**248** (equiv.)	**Catalyst** (equiv.)	**Solvent**	**Results**
1	1.0	1.1	$Pd(PPh_3)_4$ (0.15), LiCl (2.2)	DMF	— [a]
2	1.0	1.0	$Pd(PPh_3)_4$ (0.15), CuI (0.75)	DMF	11.5% [b]
3	1.0	3.0	$Pd(PPh_3)_4$ (0.15), CuI (3.0)	DMF	14.7% [b]

[a] No product isolated.
[b] Yield determined by GC-MS.

Entry 1, which we performed in the presence of lithium chloride, resulted in no product formation. Analysis of the crude product mixture revealed the presence of unreacted stannane **248**, providing further evidence that the alkynyl iodide undergoes side reactions before reacting with stannane **248**. Entry 2, performed in the presence of 0.75 equivalents of copper (I) iodide, provided the desired enyne **251** in 11.5% yield by GC-MS, with the absence of remaining iodide. Entry 3 used analogous conditions, with an increase of stannane **248** to 3.0 equivalents, and an increase of copper (I) iodide to 3.0 equivalents. This merely boosted the yield to 14.7%.

Chromatography of enyne **251** furnished a trace of product, less than what was present in the crude ^{1}H NMR. This brought us to the conclusion that **251** is quite volatile. We therefore decided to instead perform these couplings with iodide **247** in the hope that this would produce an involatile enyne cross-coupling product. Table 4 shows the results of a series of cross-couplings using iodide **247** and stannane **248**.

Table 4. Direct Cross-Coupling of **247** and **248**.



247 **248** **255**

Entry	**247** (equiv.)	**248** (equiv.)	**Catalyst** (equiv.)	**Solvent**	**Yield**
1	1.13	1.0	$Pd(PPh_3)_4$ (0.13), CuI (0.73)	DMF	24% [a]
2	1.13	1.0	$Pd(PPh_3)_4$ (0.13), CuI (1.33)	DMF	25% [a]
3 [b]	1.0	1.35	$Pd(PPh_3)_4$ (0.13), CuI (0.73)	DMF	25% [a]; 20% [c]
4	1.0	1.0	$Pd(PPh_3)_4$ (0.2)	DMF	6.5% [a]; 7.5% [c]
5 [d]	1.0	1.35	$Pd(PPh_3)_4$ (0.2), CuI (1.0)	DMF	32% [a]

[a] Yield determined by GC-MS.
[b] **247** was added to reaction as a 0.25M solution in DMF at a rate of 0.02 mL/min over 2 hours.
[c] Yield determined by ^{1}H NMR using an internal standard of anhydrous DMF.
[d] Ran at 0°C in reduced light; added solution of **247** in DMF dropwise over 2 hours.

Entry 1 was run using nearly the same conditions as used in entry 2 of Table 3, and resulted in a 24% yield, a considerable improvement. Entry 2 was conducted using 1.33 equivalents of copper (I) iodide and resulted in a 25% yield, almost no change from entry 1. Entry 3 was run using the same conditions as reaction 1, except iodide **247** was added to the reaction slowly over 2 hours. This resulted in 25% yield by GC-MS; a ^{1}H NMR ran using an internal standard indicated a yield of 20%.

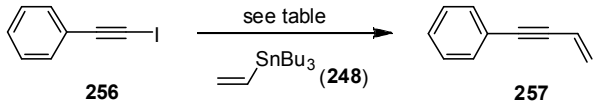
Entry 4 was performed in the absence of cocatalytic copper (I) iodide, resulting in a yield of 6.5%, which was confirmed accurate by ^{1}H NMR using an internal standard. This experiment verified that the use of copper (I) iodide increases the yield of the coupling reaction.

Entry 5 was run using an excess of stannane **248**, 1.0 equivalent of copper (I) iodide, and 0.2 equivalents of tetrakis(triphenylphosphine) palladium (0) at 0°C in the dark. The iodide was added dropwise over 2 hours. The yield showed a marked increase to 32%. However, a GC-MS of the crude product mixture taken prior to concentration *in vacuo* indicated the area of the product peak *decreased* after concentration; this led us to

conclude that the enyne **255** is also a volatile coupling product, and that iodide **247** was thus unsuitable for further optimization studies.

We therefore decided to synthesize 1-iodophenylacetylene (**256**) as our coupling partner, believing the incorporation of aromaticity into the enyne product would reduce its volatility. Table 5 shows our results.

Table 5. Direct Cross-Coupling of **256** and **248**.



256 **257**

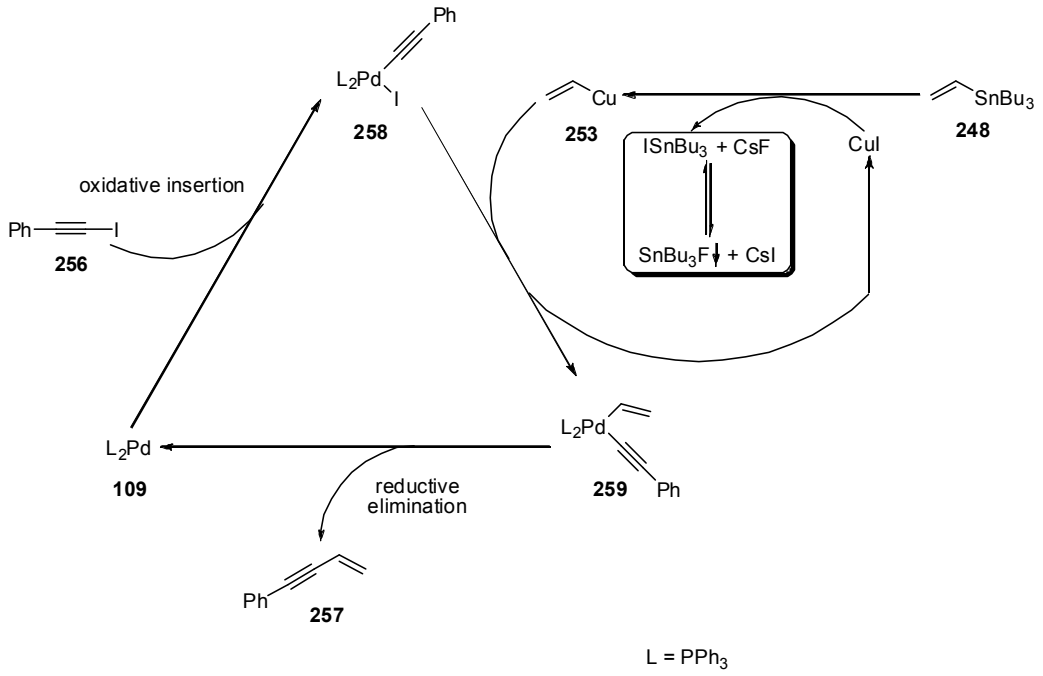
Entry	**256** (equiv.)	**248** (equiv.)	**Catalyst** (equiv.)	**Solvent**	**Yield**
1 [a]	1.13	1.0	$Pd(PPh_3)_4$ (0.2), CuI (2.0)	DMF	35% [b]
2 [a]	1.13	1.0	$Pd(PPh_3)_4$ (0.2), CuI (1.0), CsF (1.0)	DMF	25% [b]

[a] Ran at 0°C in reduced light; added solution of **256** in DMF dropwise over 2 hours
[b] Yield determined by GC-MS.

Entry 1 resulted in a 35% yield, suggesting a lower volatility of **257** as compared to **255**. However, the GC-MS indicated the product peak had decreased in area after concentration in vacuo as compared to its area before concentration, indicating volatility once again.

Entry 2 was performed using cesium (I) fluoride[373], an additive sometimes used to promote the Stille coupling reaction. In our case, it seemed to exert the opposite effect, giving a yield of 25%. Scheme 72 shows the mechanism of this promotion.

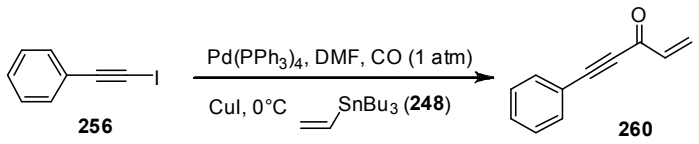
Scheme 72. Mechanism of Stille Coupling Promotion by Cesium Fluoride.



Cesium fluoride converts the tributyltin iodide transmetallation side product into tributyltin fluoride, which is insoluble in the reaction solvent and thus precipitates out of solution. The equilibrium is continually shifted to the right, and the transmetallation step is therefore promoted by virtue of LeChatelier's Principle.

Due to the presumed volatility of **257**, we decided to test the carbonylative coupling reaction using the best conditions developed thus far, in the hopes that the ketone product would be less volatile and higher-yielding (Scheme 73).

Scheme 73. Carbonylative Cross-Coupling of **256** with **248**.

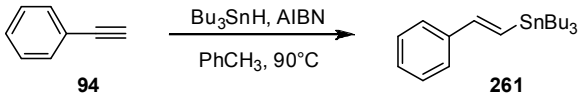


No product was isolated or detected in the reaction.

2.3 Synthesis of an Involatile Coupling Partner

Based on these results, we pursued the synthesis of a heavier stannane coupling partner that would decrease the volatility of the product. Scheme 74 shows the AIBN-initiated free-radical hydrostannation of phenylacetylene (**94**) based on a precedented procedure[374].

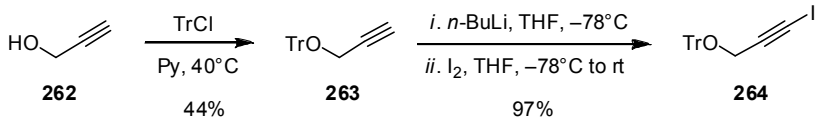
Scheme 74. Hydrostannation of Phenylacetylene.



After 4 attempts of the reaction using minor variations, very little product was generated; when the reaction did occur, the major product was hexabutyldistannane.

We then turned our attention back to synthesizing a heavy iodide coupling partner. Propargyl alcohol was triphenylmethylated using chlorotriphenylmethane to provide trityl ether **263**, then iodinated to provide iodoalkyne **264** (Scheme 75).

Scheme 75. Synthesis of Iodoalkyne **264**.



This coupling partner will increase the molecular weight of the enyne product, and should therefore eliminate further volatility issues. Additionally, the enyne should have a strong UV chromophore making reaction tracking and purification easier.

3.0 Conclusions

In summary, the development and initial optimization of a palladium-catalyzed carbonylative cross-coupling of alkenyl stannanes and alkynyl iodides has been explored. Our studies have:

1. Revealed that the alkynyl iodide undergoes side reactions which lower the yield;
2. Established that tetrakis(triphenylphosphine) palladium (0) is thus far the optimal catalyst used in the direct Stille coupling;
3. Demonstrated that copper (I) iodide cocatalyst increases the yield of the direct Stille coupling considerably;
4. Shown that *N,N*-dimethylformamide is the optimal solvent used thus far in the direct Stille coupling;
5. Exemplified that conducting the direct Stille coupling at 0°C in the absence of light with dropwise addition of the iodide increases the yield;
6. Identified the problem of enyne product volatility and synthesized an involatile coupling partner for future optimization studies.

4.0 Future Work

It is suggested that future studies focus first on the optimization of the direct Stille coupling. Performing the coupling with involatile, strongly UV-absorbing coupling partner **264** may allow accurate yields to be obtained, and should also simplify purification. Further screening of the following parameters are recommended:

- Catalysts: $Pd_2(dba)_3$ and other Pd(II) catalysts;
- Ligands: $AsPh_3$, PPh_3
- Additives/cocatalysts: CsF, LiCl
- Solvents: *N*-methylpyrrolidinone, *N,N*-dimethylacetamide

After optimization of the Stille coupling, carbon monoxide pressure will be applied, and the carbonylation conditions may be optimized by varying the following parameters:

- Carbon monoxide pressure: 1 atm, 5 atm, 15 atm, 25 atm, 40 atm, 80 atm.
- Reaction temperature: 0°C, 25°C, 50°C, 90°C.

After optimization of the carbonylation conditions, a range of high-molecular weight coupling partners can be coupled using these conditions.

General Procedures

All non-aqueous reactions were performed in oven or flame-dried glassware under an argon atmosphere and were stirred magnetically unless otherwise specified. All reagent transfers were conducted via syringe or cannula as noted and were introduced to the reaction through a rubber septum. Temperatures, other than room temperature, refer to bath temperatures. All distillations were performed under an argon atmosphere or at reduced pressure attained by either a water aspirator (10-20 mm Hg) or a mechanical pump (<1 mm Hg).

The phrase "concentrated *in vacuo*" indicates that the removal of solvent was performed by means of a Buchi rotary-evaporator attached to a water aspirator (15-30 mm Hg) followed by pumping with a mechanical bench pump (<1 mm Hg).

Chromatography

Purification by flash chromatography was performed using the indicated solvent system on EM reagent silica gel 60 (230-400) mesh. Analytical thin layer chromatography (TLC) was performed using EM silica gel 60 F-254 pre-coated glass plates (0.25 mm). Visualization was effected by short-wave UV illumination or by dipping the plate into a solution of *p*-anisaldehyde, ceric ammonium molybdate, or potassium permanganate, followed by heating on a hot plate. These stains were prepared as described below:

***p*-Anisaldehyde** was prepared by mixing 15 mL *p*-anisaldehyde, 3 mL glacial acetic acid, and 10 mL concentrated H_2SO_4 in 260 mL of 95% ethanol.

Ceric ammonium molybdate was prepared by mixing 0.2 g cerium sulfate, 4.8 g ammonium molybdate, and 10 mL concentrated H_2SO_4 in 90 mL water.

Potassium permanganate was prepared by mixing 6 g of potassium permanganate, 40 g potassium carbonate, and 10 mL of 5% sodium hydroxide. The mixture was diluted to 1 L with water.

Reagents and Solvents

Reagent grade solvents were used without purification for all extractions and work-up procedures. Deionized water was used for all aqueous reactions, work-ups, and for the preparation of all aqueous solutions. Reaction solvents were dried and purified according to published literature procedures by distillation under argon or vacuum from an appropriate drying agent.

Distilled from sodium benzophenone ketyl:

Tetrahydrofuran (THF)

Distilled from calcium hydride:

N,N-Dimethylformamide (DMF), hexanes, methylene chloride (CH_2Cl_2), pyridine, toluene.

Copper (I) iodide was purified according to a literature procedure. All other starting materials were commercially available reagents and used without further purification unless otherwise noted.

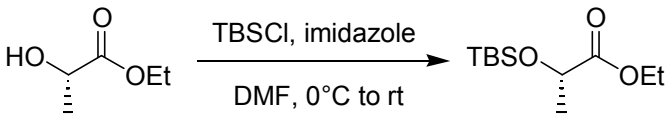
Physical Data

Proton nuclear magnetic resonance (NMR) spectra were obtained on a Bruker 300 (300 MHz, RIT) or a Bruker 300 (300 MHz, University of Rochester) nuclear magnetic resonance spectrometer. Carbon-13 NMR spectra were obtained on a Bruker 300 (75.5 MHz, RIT) nuclear magnetic resonance spectrometer. Chemical shifts are reported in ppm (δ) downfield relative to trimethylsilane and are referenced to the deuterated solvent ($CDCl_3$ at 7.26 ppm). Data are reported as follows: chemical shift (multiplicity, coupling constants in Hertz, number of hydrogens). Multiplicity is designated using the following abbreviations and combinations: s (singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet and/or multiple resonances).

Infrared (IR) spectra were collected on a BioRad FTS 3000 FTIR spectrophotometer and are reported in wave numbers (cm^{-1}) with polystyrene as a standard. Mass spectra were obtained using a Hewlett Packard 5973 MSD mass spectrometer using EI methods and methanol as a solvent.

Experimentals

2-(tert-Butyl dimethylsilanyloxy)-propionic acid ethyl ester (71):

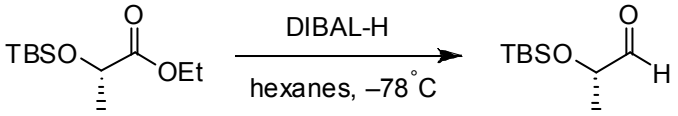


70 **71**

To a mixture of 2-hydroxypropionic acid ethyl ester (**70**) (4.76 mL, 42 mmol) and imidazole (4.3 g, 42 mmol) in *N,N*-dimethylformamide (2.1 mL) at 0°C was added *tert*-butyl dimethylsilyl chloride (6.6 g, 44 mmol) in three portions. The solution was stirred to RT overnight. The resulting white slurry was diluted with water (12 mL) and extracted with hexanes (2 x 20 mL). The combined hexane layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give **71** (8.9 g, 90%) as a colorless oil having identical spectral characteristics to that which is reported in the literature[170].

^{1}H NMR: ($CDCl_3$, 300 MHz): δ 4.27 (q, *J* = 7.2 Hz, 1H), 4.12 (m, 2H), 1.36 (d, *J* = 6.6 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H), 0.82 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H).

2-(tert-Butyl dimethyl silanyloxy)-propionaldehyde (72):

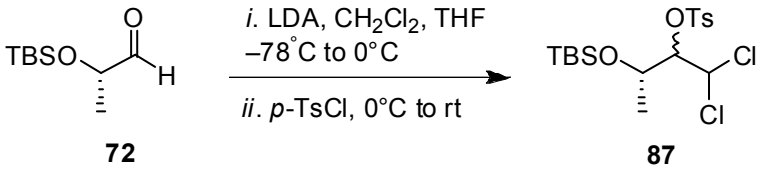


71 **72**

To a solution of ethyl ester **71** (1.22 g, 5.24 mmol) in hexanes (21 mL) at –78°C was added a 1M solution of DIBAL-H in toluene (5.2 mL, 5.4 mmol) dropwise over 10 minutes. The solution was stirred at –78°C for 2 hours, then quenched with methanol (0.7 mL). The solution was stirred for an additional 15 minutes, then warmed to RT. The reaction was added to a round-bottom flask containing a saturated aqueous solution of sodium potassium tartrate (11 mL) and stirred vigorously overnight. The biphasic mixture was partitioned, and the aqueous layer extracted with hexanes (2 x 40 mL). The combined organic layers were washed with brine (40 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a yellow oil. The oil was distilled (<20 mm Hg, 100 °C bath temperature) to afford the pure aldehyde **72** (677 mg, 68%) as a colorless oil having identical spectral characteristics to that which is reported in the literature[170].

^{1}H NMR ($CDCl_3$, 300 MHz): δ 9.62 (d, *J* = 1.2 Hz, 1H), 4.07 (m, 1H), 1.23 (d, *J* = 6.9 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H).

Toluene-4-sulfonic acid 2-(tert-butyl dimethyl silanyloxy)-1-dichloromethyl propyl ester (88):

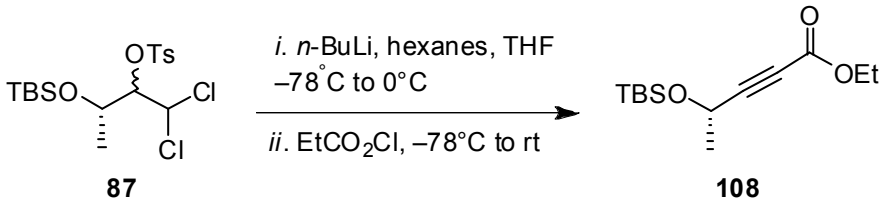


72 **87**

To a solution of diisopropylamine (4.5 mL, 51 mmol) in THF (33 mL) at 0°C was added a 0.95 M solution of *n*-BuLi in hexanes (50 mL, 48 mmol) dropwise over 15 minutes. To a second flask containing a solution of **72** (6.0 g, 32 mmol) and CH_2Cl_2 (6.1 mL) in THF (50 mL) at –78°C was added via cannula the first solution slowly over 10 minutes. The resulting yellow solution was stirred at –78°C for 30 minutes, then warmed to 0 °C over 30 minutes. To the resulting brown solution was added *p*-toluenesulfonyl chloride (6.1 g, 32 mmol) in one portion, and the mixture was stirred to RT overnight. The solution was quenched with water (1 mL) and stirred for 30 minutes. The biphasic mixture was partitioned, and the organic layer was washed with aqueous 10% HCl (50 mL) and aqueous 1M NaOH (50 mL). The aqueous layers were each back-extracted with Et_2O (2 x 50 mL) and the combined organics washed with brine, dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude **87** (0.71 g) as a brown oil having identical spectral characteristics to that which is reported in the literature[170].

^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.83-7.82 (dd, *J* = 8.4, 5.4 Hz, 4H), 7.32 (d, *J* = 8.4 Hz, 4H), 6.01 (d, *J* = 2.4 Hz, 1H), 5.82 (d, *J* = 6.3 Hz, 1H), 4.77-4.73 (dd, *J* = 7.5, 2.2 Hz, 1H), 4.71-4.70 (dd, *J* = 6.3, 3.3 Hz, 1H), 4.36-4.32 (m, 1H), 4.09-4.02 (m, 1H), 2.44 (s, 6H), 1.30 (d, *J* = 6.0 Hz, 3H), 1.25 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 18H), 0.08 (s, 6H), 0.07 (s, 6H).

4-(tert-Butyl dimethyl silanyloxy)-pent-2-ynoic acid ethyl ester (108):



87 **108**

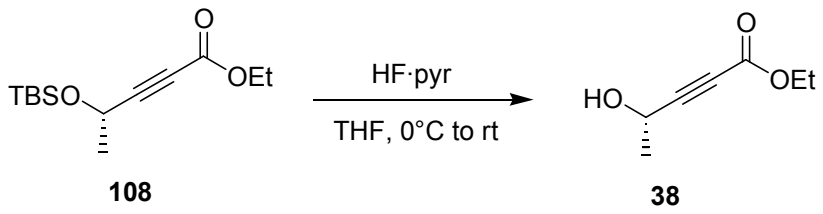
To a solution of purified **87** (0.70 g, 1.63 mmol) in THF (6 mL) at –78°C was added a 2.33 M solution of *n*-BuLi in hexanes (2.3 mL, 5.4 mmol) dropwise over 10 minutes. The resulting yellow solution was stirred at –78°C for 30 minutes, then warmed to 0°C over 45 minutes. The resulting orange suspension was cooled to –78°C, and ethyl chloroformate (1.86 mL, 1.96 mmol) was added dropwise over 10 minutes. Reaction was warmed to RT over 2 hours. The mixture was diluted with a saturated solution of aqueous ammonium chloride (25 mL), brine (20 mL), and water (15 mL). The aqueous mixture was then extracted with Et_2O (50 mL) and CH_2Cl_2. The combined organics were dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford crude **108** (0.92 g) as a clear oil having identical spectral characteristics to that which is reported in the literature[375].

IR (cm^{-1}) 2928, 2857, 2243, 1714, 1239.

^{1}H NMR ($CDCl_3$, 300 Hz): 4.63 (q, J = 6.6 Hz, 1H), 4.25 (q, J = 7.2 Hz, 2H), 1.41 (d, J = 6.6 Hz, 3H), 0.92 (s, 9H), 0.20 (s, 3H), 0.15 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 Hz): 154.0, 89.5, 62.4, 59.1, 30.1, 26.1, 24.8, 18.5, 14.4, -4.6, -4.7.

4-Hydroxy pent-2-ynoic acid ethyl ester (38):



108 **38**

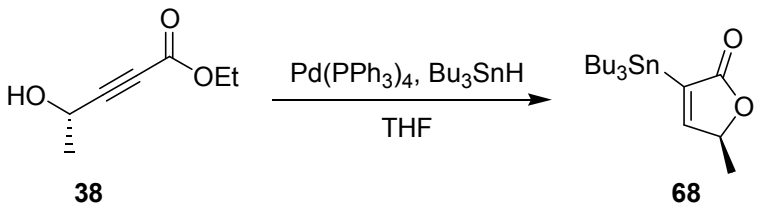
To a solution of **108** (0.38 g, 0.81 mmol) in THF (6 mL) at 0°C was added a 70% solution of hydrogen fluoride-pyridine complex (0.71 mL, 27.5 mmol) dropwise over 10 minutes. After complete addition, the solution was warmed to RT over 2.5 h. The solution was slowly quenched with saturated aqueous sodium bicarbonate (100 mL), and extracted with Et_2O (35 mL) and CH_2Cl_2 (2 x 25 mL). The combined organics were washed with saturated aqueous copper (II) sulfate (25 mL) and brine (25 mL), then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel eluting with a gradient of 99:1–85:15 hexanes/ethyl acetate to afford **38** (134 mg, 57% over 2 steps) as a clear oil having identical spectral characteristics to that which is reported in the literature[110].

IR (cm^{-1}) 3400, 2914, 2840, 2240, 1695, 1239.

^{1}H NMR ($CDCl_3$, 300 Hz): 4.65 (q, J = 6.9 Hz, 1H), 4.24 (q, J = 7.2 Hz, 2H), 1.74 (s, 1H), 1.49 (d, J = 6.6 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H).

^{13}C NMR ($CDCl_3$, 75 Hz): 153.8, 88.5, 62.6, 58.5, 30.1, 23.7, 14.4.

5-Methyl-3-tributylstannanyl-5H-furan-2-one (68):



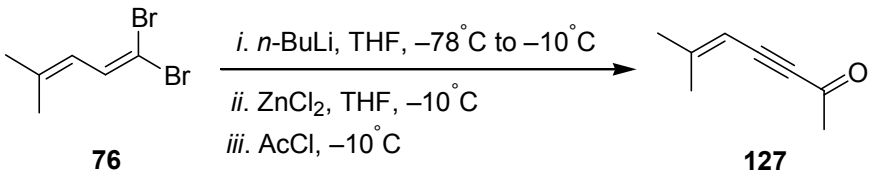
38 **68**

To a solution of **38** (0.080 g, 0.56 mmol) and tetrakis(triphenylphosphine) palladium (0) (0.065 g, 0.056 mmol) in THF (0.56 mL) was added a solution of tributyltin hydride (0.17 mL, 0.62 mmol) in THF (0.56 mL) dropwise over 5 minutes. Reaction flask was covered with aluminum foil and stirred at RT for 4 h. The yellow mixture was concentrated under reduced pressure, diluted with *n*-pentane (100 mL), and cooled to –10°C. The suspension was stirred for 1 h, filtered, and concentrated *in vacuo*. The resulting pale yellow oil was chromatographed on silica gel eluting with a gradient of 100:0–98:2 *n*-pentane/ethyl acetate to afford **68** (150 mg, 68%) as a pale yellow oil having identical spectral characteristics to that which is reported in the literature[142].

IR (cm^{-1}) 2921, 1731, 1143.

^{1}H NMR ($CDCl_3$, 300 Hz): 7.44 (d, J = 1.5 Hz, 1H), 5.05 (m, 1H), 1.49 (m, 6H), 1.40 (d, J = 6.0 Hz, 1H), 1.31 (m, 6H), 1.07 (m, 6H), 0.89 (t, J = 7.2 Hz, 9H).

6-Methyl hept-5-en-3-yn-2-one (7):



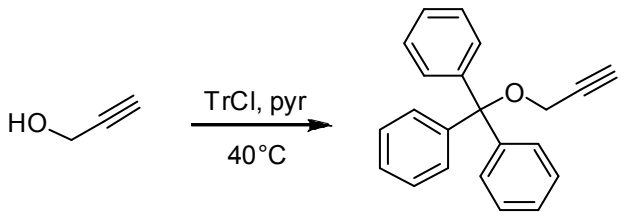
76 **127**

To a solution of **76** (0.395 g, 1.65 mmol) in THF (1 mL) at –78°C was added n-BuLi in hexanes (1.3 mL, 3.5 mmol) dropwise. The orange slurry was stirred for 10 minutes, warmed to –10°C, and stirred for another 25 minutes. A solution of zinc chloride (0.25 g) in THF (2 mL) was added dropwise, and the solution stirred at –10°C for 30 minutes. Acetyl chloride was then added dropwise, and the solution stirred for 40 minutes. The reaction mixture was diluted with diethyl ether (50 mL), a saturated aqueous solution of sodium bicarbonate (30 mL), brine (10 mL), and water (20 mL). The organic layer was partitioned, and the aqueous layer extracted with diethyl ether (3 x 40 mL). The combined organics were washed with brine (10 mL), dried over anhydrous magnesium sulfate, filtered, and *in vacuo*. The resulting orange oil was chromatographed on silica gel eluting with a gradient of 100:0–98:2 hexanes/ethyl acetate to afford **127** (108 mg, 54%) as a pale yellow oil.

IR (cm^{-1}) 2921, 1731, 1143.

^{1}H NMR ($CDCl_3$, 300 Hz): 5.41 (s, 1H), 2.37 (s, 3H), 1.99 (s, 3H), 1.90 (s, 3H).

(Diphenyl prop-2-ynyloxy methyl) benzene (263):



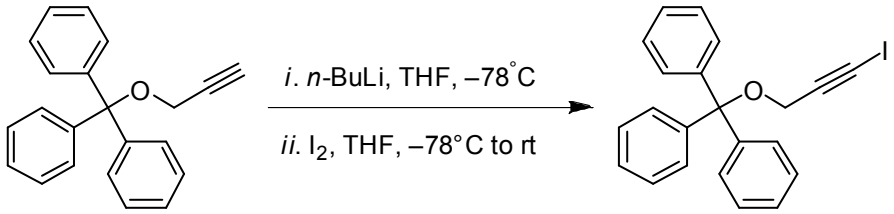
262 **263**

To a solution of **262** (0.52 mL, 9.0 mmol) in pyridine (7.0 mL) was added chlorotriphenylmethane (2.74 g, 10.0 mmol) and the solution stirred at 40°C for 16 h. The reaction mixture was concentrated *in vacuo*, dissolved in ethyl acetate (70 mL), and washed with water (80 mL). The aqueous layer was extracted with ethyl acetate (2 x 50 mL) and the combined organics concentrated *in vacuo*. The resulting beige solid was chromatographed[376] on silica gel eluting with with a gradient of 97:0:3–95:2:3 hexanes/ethyl acetate/triethylamine to afford **263** as a white solid (1.2 g, 44%[377]).

IR (cm^{-1}) 3290.8, 3057.2, 2870.2, 2126.3, 1446.9, 1054.8, 696.8.

^{1}H NMR ($CDCl_3$, 300 Hz): 7.48-7.45 (dd, J = 6.9 Hz, 1.7 Hz, 6H), 7.34-7.23 (m, 9H), 3.75 (d, J = 2.4 Hz, 2H), 2.39 (d, J = 2.4 Hz, 1H).

Representative Procedure for Iodination of Terminal Alkynes: [Diphenyl-(3-iodo prop-2-ynyloxy) methyl] benzene (264):



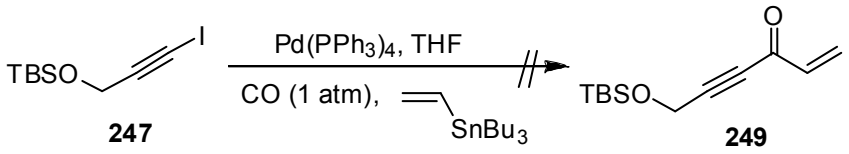
263 **264**

To a solution of **263** (1.17 g, 3.9 mmol) in THF (8.0 mL) at –78°C in a 3-neck flask affixed with two addition funnels was added a 2.3 M solution of *n*-BuLi in hexanes (1.74 mL, 4.0 mmol) dropwise via addition funnel over 30 minutes. The resulting pink solution was stirred at –78°C for 30 minutes, then a solution of iodine (1.2 g, 4.7 mmol) in THF (8.0 mL) was added dropwise via addition funnel over 30 minutes. The yellow slurry was stirred to room temperature over 16 h. The reaction mixture was diluted with diethyl ether (50 mL) and washed with a saturated aqueous solution of sodium metabisulfite (3 x 25 mL) and brine (20 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to afford **264** as a beige solid (1.6 g, 97%).

IR (cm^{-1}) 3058.8, 2893.2, 2850.8, 2193.1, 1443.8, 1064.7, 694.4.

^{1}H NMR ($CDCl_3$, 300 Hz): 7.48-7.45 (dd, J = 6.9 Hz, 1.7 Hz, 6H), 7.34-7.23 (m, 9H), 3.92 (s, 1H).

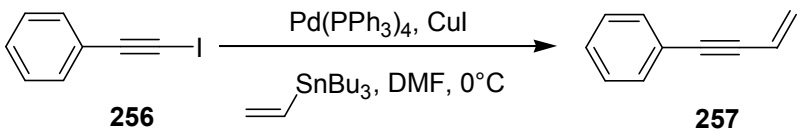
Representative Carbonylation Procedure: 6-(*tert*-Butyl dimethyl silanyloxy)-hex-1-en-4-yn-3-one (249):



247 **249**

A solution of tetrakis(triphenylphosphine) palladium (0) (78 mg, 0.067 mmol) in THF (2.7 mL) was sparged with carbon monoxide for 15 minutes. Iodide **247** (0.2 g, 0.67 mmol) was added via syringe, and the solution sparged with carbon monoxide for 1 minute. Tributylvinyltin (0.22 mL, 0.74 mmol) was added via syringe, and the reaction was stirred at room temperature under a carbon monoxide atmosphere for 3 h. The reaction mixture was concentrated under reduced pressure to afford a red oil (415 mg), which was chromatographed on silica gel eluting with a gradient of 100:0–0:100 hexanes/ethyl acetate. Multiple unidentifiable impure and semipure products were recovered.

Representative Direct Coupling Procedure: But-3-en-1-ynyl benzene (257):



To an aluminum-covered, argon-purged flask was added tetrakis(triphenylphosphine) palladium (0) (75 mg, 0.064 mmol), copper (I) iodide (62 mg, 0.32 mmol), and pre-argon sparged DMF (0.9 mL). To the resulting black mixture was added tributylvinyltin (0.13 mL, 0.44 mmol) via syringe. The reaction was sparged for 5 minutes, then cooled to 0°C. A solution of **256** (75 mg, 0.32 mmol) in pre-argon sparged DMF (0.9 mL) was added dropwise over 2 h. The reaction was stirred to room temperature over 16 h. The resulting black mixture was diluted with diethyl ether (40 mL) and a saturated aqueous solution of potassium fluoride (40 mL) and stirred vigorously for 2 h. The layers were partitioned, and the organic layer washed with a 5% aqueous solution of lithium chloride (3 x 20 mL), brine (20 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford crude **257** (205 mg, 35%[378]).

GC-MS: m/e: 128 [M] (100%); 102 [M-26] (22%).
^{1}H NMR ($CDCl_3$, 300 Hz): 7.44 (m, 2H), 7.32 (m, 3H), 6.03 (dd, J = 17.4, 11.2 Hz, 1H), 5.74 (dd, J = 17.4, 2.2 Hz, 1H), 5.55 (dd, J = 11.2, 2.2 Hz, 1H).

References

(1) Faulkner, D. J. *Nat. Prod. Rep.* **2001**, *18*, 1-49.

(2) Ciereszko, L. S.; Kraus, T. K. In *Biology and Geology of Coral Reefs*; Jones, O. A., Endean, R., Eds.; Academic: New York, 1973; Vol. 2, p 183-203.

(3) Jie, M. S. F. L. K.; Pasha, M. K. *Nat. Prod. Rep.* **1998**, *15*, 607-629.

(4) Schmitz, F.; Lorance, E. D. *J. Org. Chem.* **1971**, *36*, 719-721.

(5) Schmitz, F.; Lorance, E. D.; Ciereszko, L. S. *J. Org. Chem.* **1969**, *34*, 1989-1990.

(6) Schmitz, F.; Krans, K. W.; Ciereszko, L. S.; Sifford, D. H.; Weinheimer, A. J. *Tetrahedron Lett.* **1966**, *1*, 97.

(7) Su, J.; Dai, C.; Huang, H.; Wu, Y.; P., S.; Hsu, C.; Sheu, J. *Chemical & Pharmaceutical Bulletin* **2007**, *55*, 594.

(8) Rezanka, T.; Dembitzky, V. M. *Tetrahedron* **2001**, *57*, 8743.

(9) Pattenden, G. *Prog. Chem. Org. Nat. Prod.* **1978**, *35*, 133.

(10) Ohlaff, G.; Flament, I. *Prog. Chem. Org. Nat. Prod.* **1979**, *36*, 231.

(11) 2-Furanone. http://en.wikipedia.org/wiki/2-furanone. (accessed Oct 26, 2007).

(12) Slaughter, J. *Biol. Rev.* **1999**, *74*, 259.

(13) Alali, F.; Liu, X.; McLaughlin, J. *J. Nat. Prod.* **1999**, *62*, 504.

(14) Hoppe, R.; Scharf, H.-D. *Synthesis* **1995**, *12*, 1447.

(15) Nattrass, G.; Diez, E.; McLachlan, M.; Dixon, D.; Ley, S. *Angew. Chem. Int. Ed.* **2005**, *44*, 580.

(16) Oberlies, N.; Croy, V.; Harrison, M.; McLaughlin, J. *Cancer Lett.* **1997**, *15*, 73.

(17) Zeng, L.; Ye, Q.; Oberlies, N.; Shi, G.; Gu, Z.; He, K.; McLaughlin, J. *Nat. Prod. Rep.* **1996**, *13*, 275.

(18) Strand, D.; Norrby, P.-O.; Rein, T. *J. Org. Chem.* **2006**, *71*, 1879-1891.

(19) Takahashi, S.; Kubota, A.; Nakata, T. *Org. Lett.* **2003**, *5*, 1353-1356.

(20) Strand, D.; Rein, T. *Org. Lett.* **2005**, *7*, 199.

(21) Huang, G.-r.; Jiang, S.; Wu, Y.-l.; Jin, Y.; Yao, Z.-j.; Wu, J.-r. *ChemBioChem* **2003**, *4*, 1216-1221.

(22) Hu, T.-S.; Yu, Q.; Wu, Y.-L.; Wu, Y. *J. Org. Chem.* **2001**, *66*, 853.

(23) Marshall, J. A.; Jiang, H. *J. Nat. Prod.* **1999**, *62*, 1123-1127.

(24) Naito, H.; Kawahara, E.; Maruta, K.; Maeda, M.; Sasaki, S. *J. Org. Chem.* **1995**, *60*, 4419-27.

(25) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1998**, *120*, 4017-4018.

(26) Hanessian, S.; Giroux, S.; Buffat, M. *Org. Lett.* **2005**, *7*, 3989-3992.

(27) He, Y.-T.; Xue, S.; Hu, T.-S.; Yao, Z.-J. *Tetrahedron Lett.* **2005**, *46*, 5393-5397.

(28) Takahashi, S.; Kubota, A.; Nakata, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 4751-4754.

(29) Zhu, L.; Mootoo, D. R. *Org. Biomol. Chem.* **2005**, *3*, 2750-2754.

(30) Takahashi, S.; Kubota, A.; Nakata, T. *Tetrahedron* **2003**, *59*, 1627-1638.

(31) Takahashi, S.; Kubota, A.; Nakata, T. *Tetrahedron Lett.* **2002**, *43*, 8661-8664.
(32) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3622-3626.
(33) Dixon, D. J.; Ley, S. V.; Reynolds, D. J. *Chem.--Eur. J.* **2002**, *8*, 1621-1636.
(34) Hanessian, S.; Grillo, T. A. *J. Org. Chem.* **1998**, *63*, 1049-1057.
(35) D'Souza, L. J.; Sinha, S. C.; Lu, S. F.; Keinan, E.; Sinha, S. C. *Tetrahedron* **2001**, *57*, 5255-5262.
(36) Sinha, S. C.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1999**, *64*, 7067-7073.
(37) Zeng, B.-B.; Wu, Y.; Yu, Q.; Wu, Y.-L.; Li, Y.; Chen, X.-G. *Angew. Chem., Int. Ed.* **2000**, *39*, 1934-1937.
(38) Jiang, S.; Li, Y.; Chen, X.-G.; Hu, T.-S.; Wu, Y.-L.; Yao, Z.-J. *Angew. Chem., Int. Ed.* **2004**, *43*, 329-334.
(39) Zeng, B.-B.; Wu, Y.; Jiang, S.; Yu, Q.; Yao, Z.-J.; Liu, Z.-H.; Li, H.-Y.; Li, Y.; Chen, X.-G.; Wu, Y.-L. *Chem.--Eur. J.* **2003**, *9*, 282-290.
(40) Jiang, S.; Liu, Z.-H.; Sheng, G.; Zeng, B.-B.; Cheng, X.-G.; Wu, Y.-L.; Yao, Z.-J. *J. Org. Chem.* **2002**, *67*, 3404-3408.
(41) Wang, T.-L.; Hu, X. E.; Cassady, J. M. *Tetrahedron Lett.* **1995**, *36*, 9301-9304.
(42) Wang, M.; Chen, Y.; Lou, L.; Tang, W.; Wang, X.; Shen, J. *Tetrahedron Lett.* **2005**, *46*, 5309-5312.
(43) Sinha, S. C.; Sinha, A.; Sinha, S. C.; Keinan, E. *J. Am. Chem. Soc.* **1997**, *119*, 12014-12015.
(44) Jiang, S.; Wu, Y.-L.; Yao, Z.-J. *Chin. J. Chem.* **2002**, *20*, 1393-1400.
(45) Jiang, S.; Wu, Y.-L.; Yao, Z.-J. *Chin. J. Chem.* **2002**, *20*, 692-696.
(46) Baurle, S.; Hoppen, S.; Koert, U. *Angew. Chem., Int. Ed.* **1999**, *38*, 1263-1266.
(47) Hoppen, S.; Baurle, S.; Koert, U. *Chem.--Eur. J.* **2000**, *6*, 2382-2396.
(48) Sinha, S. C.; Sinha-Bagchi, A.; Yazbak, A.; Keinan, E. **1995**, *36*, 9257-9260.
(49) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1771-1779.
(50) Avedissian, H.; Sinha, S.; Yazbak, A.; Sinha, A.; Neogi, P.; Sinha, S.; Keinan, E. *J. Org. Chem.* **2000**, *65*, 6035-6051.
(51) Zhao, H.; Gorman, J. S. T.; Pagenkopf, B. L. *Org. Lett.* **2006**, *8*, 4379-4382.
(52) Zhu, L.; Mootoo, D. R. *J. Org. Chem.* **2004**, *69*, 3154-3157.
(53) Bandur, N. G.; Brueckner, D.; Hoffmann, R. W.; Koert, U. *Org. Lett.* **2006**, *8*, 3829-3831.
(54) Tominaga, H.; Maezaki, N.; Yanai, M.; Kojima, N.; Urabe, D.; Ueki, R.; Tanaka, T. *Eur. J. Org. Chem.* **2006**, 1422-1429.
(55) Maezaki, N.; Kojima, N.; Sakamoto, A.; Tominaga, H.; Iwata, C.; Tanaka, T.; Monden, M.; Damdinsuren, B.; Nakamori, S. *Chem.--Eur. J.* **2003**, *9*, 389-399.
(56) Maezaki, N.; Kojima, N.; Sakamoto, A.; Iwata, C.; Tanaka, T. *Org. Lett.* **2001**, *3*, 429-432.

(57) Keum, G.; Hwang, C. H.; Kang, S. B.; Kim, Y.; Lee, E. *J. Am. Chem. Soc.* **2005**, *127*, 10396-10399.

(58) Schaus, S. E.; Brnalt, J.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 4876-4877.

(59) Yoshimitsu, T.; Makino, T.; Nagaoka, H. *J. Org. Chem.* **2004**, *69*, 1993-1998.

(60) Narayan, R. S.; Borhan, B. *J. Org. Chem.* **2006**, *71*, 1416-1429.

(61) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Tanaka, T. *Chem. Commun. (Cambridge, U. K.)* **2004**, 406-407.

(62) Maezaki, N.; Tominaga, H.; Kojima, N.; Yanai, M.; Urabe, D.; Ueki, R.; Tanaka, T.; Yamori, T. *Chem.--Eur. J.* **2005**, *11*, 6237-6245.

(63) Zhang, Q.; Lu, H.; Richard, C.; Curran, D. P. *J. Am. Chem. Soc.* **2004**, *126*, 36-37.

(64) Takahashi, S.; Ogawa, N.; Koshino, H.; Nakata, T. *Org. Lett.* **2005**, *7*, 2783-2786.

(65) Makabe, H.; Tanaka, A.; Oritani, T. *J. Chem. Soc. Perkin Trans. 1* **1994**, *14*, 1975-1981.

(66) Sinha, S.; Keinan, E. *J. Am. Chem. Soc.* **1993**, *115*, 4891-4892.

(67) Tam, Y.-T.; Chaboche, C.; Figadere, B.; Chappe, B.; Hieu, B.-C.; Cave, A. *Tetrahedron Lett.* **1994**, *35*, 883-886.

(68) Quinn, K.; Isaacs, A.; DeChristopher, B.; Szklarz, S.; Arvary, R. *Org. Lett.* **2005**, *7*, 1243-1245.

(69) Koert, U. *Tetrahedron Lett.* **1994**, *35*, 2517-2520.

(70) Prestat, G.; Baylon, C.; Heck, M.-P.; Grasa, G. A.; Nolan, S. P.; Mioskowski, C. *J. Org. Chem.* **2004**, *69*, 5770-5773.

(71) Emde, U.; Koert, U. *Eur. J. Org. Chem.* **2000**, 1889-1904.

(72) Emde, U.; Koert, U. *Tetrahedron Lett.* **1999**, *40*, 5979-5982.

(73) Franck, X.; Figadere, B.; Cave, A. *Tetrahedron Lett.* **1996**, *37*, 1593-1594.

(74) Quinn, K. J.; Smith, A. G.; Cammarano, C. M. *Tetrahedron* **2007**, *63*, 4881-4886.

(75) Hattori, Y.; Konno, H.; Abe, M.; Miyoshi, H.; Goto, T.; Makabe, H. *Bioorg. Med. Chem.* **2007**, *15*, 3026-3031.

(76) Sinha, S.; Sinha, A.; Yazbak, A.; Keinan, E. *J. Org. Chem.* **1996**, *61*, 7640-7641.

(77) Yazbak, A.; Sinha, S. C.; Keinan, E. *J. Org. Chem.* **1998**, *63*, 5863-5868.

(78) Marshall, J. A.; Piettre, A.; Paige, M. A.; Valeriote, F. *J. Org. Chem.* **2003**, *68*, 1780-1785.

(79) Gypser, A.; Buelow, C.; Scharf, H.-D. *Tetrahedron* **1995**, *51*, 1921-1930.

(80) Abe, M.; Murai, M.; Ichimaru, N.; Kenmochi, A.; Yoshida, T.; Kubo, A.; Kimura, Y.; Moroda, A.; Makabe, H.; Nishioka, T.; Miyoshi, H. *Biochemistry* **2005**, *44*, 14898-14906.

(81) Marshall, J. A.; Sabatini, J. J.; Valeriote, F. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2434-2437.

(82) Motoyama, T.; Yabunaka, H.; Miyoshi, H. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2089-2092.

(83) Konno, H.; Hiura, N.; Makabe, H.; Abe, M.; Miyoshi, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 629-632.
(84) Abe, M.; Kenmochi, A.; Ichimaru, N.; Hamada, T.; Nishioka, T.; Miyoshi, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 779-782.
(85) Konno, H.; Makabe, H.; Tanaka, A.; Oritani, T. *Biosci., Biotechnol., Biochem.* **1995**, *59*, 2355-2357.
(86) Han, H.; Sinha, M. K.; D'Souza, L. J.; Keinan, E.; Sinha, S. C. *Chem.--Eur. J.* **2004**, *10*, 2149-2158.
(87) Hoye, T. R.; Hanson, P. R.; Kovelesky, A. C.; Ocain, T. D.; Zhuang, Z. *J. Am. Chem. Soc.* **1991**, *113*, 9369-9371.
(88) Curran, D. P.; Zhang, Q.; Richard, C.; Lu, H.; Gudipati, V.; Wilcox, C. S. *J. Am. Chem. Soc.* **2006**, *128*, 9561-9573.
(89) Fujita, D.; Ichimaru, N.; Abe, M.; Murai, M.; Hamada, T.; Nishioka, T.; Miyoshi, H. *Tetrahedron Lett.* **2005**, *46*, 5775-5779.
(90) Das, S.; Li, L.-S.; Abraham, S.; Chen, Z.; Sinha, S. C. *J. Org. Chem.* **2005**, *70*, 5922-5931.
(91) Gudipati, V.; Curran, D. P.; Wilcox, C. S. *J. Org. Chem.* **2006**, *71*, 3599-3607.
(92) Makabe, H.; Hattori, Y.; Tanaka, A.; Oritani, T. *Org. Lett.* **2002**, *4*, 1083-1085.
(93) Makabe, H.; Hattori, Y.; Kimura, Y.; Konno, H.; Abe, M.; Miyoshi, H.; Tanaka, A.; Oritani, T. *Tetrahedron* **2004**, *60*, 10651-10657.
(94) Makabe, H.; Tanaka, A.; Oritani, T. *Tetrahedron Lett.* **1997**, *38*, 4247-4250.
(95) Makabe, H.; Miyawaki, A.; Takahashi, R.; Hattori, Y.; Konno, H.; Abe, M.; Miyoshi, H. *Tetrahedron Lett.* **2004**, *45*, 973-977.
(96) Makabe, H.; Higuchi, M.; Konno, H.; Murai, M.; Miyoshi, H. *Tetrahedron Lett.* **2005**, *46*, 4671-4675.
(97) Velasco, M. A. *Synlett* **2005**, 1807-1808.
(98) Berkenbusch, T.; Bruckner, R. *Tetrahedron* **1998**, *54*, 11461-11470.
(99) Harcken, C.; Bruckner, R. *New J. Chem.* **2001**, *25*, 40-54.
(100) He, Y.-T.; Yang, H.-N.; Yao, Z.-J. *Tetrahedron* **2002**, *58*, 8805-8810.
(101) Takahashi, S.; Nakata, T. *J. Org. Chem.* **2002**, *67*, 5739-5752.
(102) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703.
(103) Takahashi, S.; Nakata, T. *Tetrahedron Lett.* **1999**, *40*, 727-730.
(104) Cotarca, L.; Delogu, P.; Nardelli, A.; Sunjic, V. *Synthesis* **1996**, 553-576.
(105) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1997**, *62*, 5989-5995.
(106) Tinsley, J. M.; Roush, W. R. *J. Am. Chem. Soc.* **2005**, *127*, 10818-10819.
(107) Marshall, J. A.; Chen, M. *J. Org. Chem.* **1997**, *62*, 5996-6000.
(108) Marshall, J. A.; Hinkle, K. W. *Tetrahedron Lett.* **1998**, *39*, 1303-1306.
(109) Tinsley, J. M.; Mertz, E.; Chong, P. Y.; Rarig, R.-A. F.; Roush, W. R. *Org. Lett.* **2005**, *7*, 4245-4248.
(110) Trost, B. M.; Muller, T. J. J.; Martinez, J. *J. Am. Chem. Soc.* **1995**, *117*, 1888-1899.
(111) Trost, B. M.; Toste, F. D. *Tetrahedron Lett.* **1999**, *40*, 7739-7743.

(112) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067-2096.

(113) Trost, B. M.; Frederiksen, M. U.; Rudd, M. T. *Angew. Chem. Int. Ed.* **2005**, *44*, 6630-6666.

(114) Head, G. D.; Whittingham, W. G.; Brown, R. C. D. *Synlett* **2004**, 1437-1439.

(115) Trost, B. M.; Calkins, T. L.; Bochet, C. G. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2632-2635.

(116) Trost, B. M.; Shi, Z. *J. Am. Chem. Soc.* **1994**, *116*, 7459-60.

(117) Trost, B. M.; Calkins, T. L. *Tetrahedron Lett.* **1995**, *36*, 6021-4.

(118) Cecil, A. R. L.; Brown, R. C. D. *Org. Lett.* **2002**, *4*, 3715-3718.

(119) Cecil, A. R. L.; Brown, R. C. D. *ARKIVOC (Gainesville, FL, U. S.)* **2001**, 49-57.

(120) Cecil, A. R. L.; Hu, Y.; Vicent, M. J.; Duncan, R.; Brown, R. C. D. *J. Org. Chem.* **2004**, *69*, 3368-3374.

(121) Hu, Y.; Brown, R. C. D. *Chem. Commun. (Cambridge, U. K.)* **2005**, 5636-5637.

(122) Donohoe, T. J.; Butterworth, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4766-4768.

(123) Goeksel, H.; Stark, C. B. W. *Org. Lett.* **2006**, *8*, 3433-3436.

(124) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2006**, *8*, 3557-3560.

(125) Hoye, T. R.; Tan, L. *Tetrahedron Lett.* **1995**, *36*, 1981-4.

(126) Hoye, T. R.; Eklov, B. M.; Jeon, J.; Khoroosi, M. *Org. Lett.* **2006**, *8*, 3383-3386.

(127) Liao, B.; Negishi, E.-i. *Heterocycles* **2000**, *52*, 1241-1249.

(128) Hoye, T. R.; Ye, Z. *J. Am. Chem. Soc.* **1996**, *118*, 1801-2.

(129) Hoye, T. R.; Tan, L. Method for the Synthesis of Bis-Tetrahydrofuranyl Annonaceous Acetogenins. US 5587491, 1996.

(130) Hoye, T. R.; Ye, Z. Synthesis of Acetogenins. US 5677467, 1997.

(131) Crimmins, M. T.; She, J. *J. Am. Chem. Soc.* **2004**, *126*, 12790-12791.

(132) Fuerstner, A.; Dierkes, T. *Org. Lett.* **2000**, *2*, 2463-2465.

(133) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369-2372.

(134) Schnurch, M.; Spina, M.; Khan, A. F.; Mihovilovic, M. D.; Stanetty, P. *Chem. Soc. Rev.* **2007**, *36*, 1046-1057.

(135) Eguchi, C.; Kakuta, A. *Bulletin of the Chemical Society of Japan* **1974**, *47*, 1704-1708.

(136) Mori, K. *Tetrahedron* **1975**, *31*, 3011-3012.

(137) Ishigami, K.; Kitahara, T. *Tetrahedron* **1995**, *51*, 6431-6442.

(138) Yang, W.-Q.; Kitahara, T. *Tetrahedron* **2000**, *56*, 1451-1461.

(139) Yang, W.-Q.; Kitahara, T. *Tetrahedron Lett.* **1999**, *40*, 7827-7830.

(140) Yang, W.-Q.; Ishigami, K.; Kitahara, T. *Proc. Jpn. Acad., Ser. B* **2001**, *77B*, 157-160.

(141) Lee, C.-L.; Lin, C.-F.; Lin, W.-R.; Wang, K.-S.; Chang, Y.-h.; Lin, S.-R.; Wu, Y.-C.; Wu, M.-J. *Bioorg. Med. Chem.* **2005**, *13*, 5864-5872.

(142) Richecoeur, A. M. E.; Sweeney, J. B. *Tetrahedron Lett.* **1998**, *39*, 8901-8904.

(143) Richecoeur, A. M. E.; Sweeney, J. B. *Tetrahedron* **2000**, *56*, 389-395.
(144) Hofman, S.; Gao, L.-J.; Van Dingenen, H.; Hosten, N. G. C.; Van Haver, D.; De Clercq, P. J.; Milanesio, M.; Viterbo, D. *Eur. J. Org. Chem.* **2001**, 2851-2860.
(145) Guerriero, A.; Meinesz, A.; D'Ambrosio, M.; Pietra, F. *Helv. Chim. Acta* **1992**, *75*, 689-695.
(146) Guerriero, A.; Marchetti, F.; D'Ambrosio, M.; Senesi, S.; Dini, F.; Pietra, F. *Helv. Chim. Acta* **1993**, *76*, 855-864.
(147) Guerriero, A.; D'Ambrosio, M. *Eur. J. Org. Chem.* **1999**, 1985-1990.
(148) Fontana, A.; Ciavatta, M. L.; Mollo, E.; Naik, C. G.; Wahidulla, S.; D'Souza, L.; Cimino, G. *J. Nat. Prod.* **1999**, *62*, 931-933.
(149) Adolph, S.; Jung, V.; Rattke, J.; Pohnert, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 2806-2808.
(150) Commeiras, L.; Santelli, M.; Parrain, J.-L. *Org. Lett.* **2001**, *3*, 1713-1715.
(151) Commeiras, L.; Bourdron, J.; Douillard, S.; Barbier, P.; Vanthuyne, N.; Peyrot, V.; Parrain, J.-L. *Synthesis* **2006**, 166-181.
(152) Commeiras, L.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* **2003**, *44*, 2311-2314.
(153) Commeiras, L.; Santelli, M.; Parrain, J.-L. *Synlett* **2002**, 743-746.
(154) Commeiras, L.; Parrain, J.-L. *Tetrahedron: Asymmetry* **2004**, *15*, 509-517.
(155) Gabriele, B.; Salerno, G. *Chem. Commun. (Cambridge)* **1997**, 1083-1084.
(156) Marshall, J. A.; DuBay, W. J. *J. Org. Chem.* **1993**, *58*, 3602-3.
(157) Kuivila, H. G. *Adv. Organomet. Chem.* **1964**, *1*, 47.
(158) Oshima, K.; Uchimoto, K. *Yuki Gosei Kagaku Kyokaishi* **1989**, *47*, 40-52.
(159) Negishi, E. *Organometallics in Organic Synthesis*; Wiley: NY, 1980; Vol. 1, pp 45, 357, and 406.
(160) Dodero, V. I.; Koll, L. C.; Faraoni, M. B.; Mitchell, T. N.; Podesta, J. C. *J. Org. Chem.* **2003**, *68*, 10087-10091.
(161) Corey, E. J.; Wollenberg, R. H. *J. Org. Chem.* **1975**, *40*, 2265-2266.
(162) Asao, N.; Liu, J.-X.; Sudoh, T.; Yamamoto, Y. *J. Org. Chem.* **1996**, *61*, 4568-4571.
(163) Zhang, H. X.; Guibe, F.; Balavoine, G. *Tetrahedron Lett.* **1988**, *29*, 619.
(164) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857-1867.
(165) Guibe, F. *Main Group Met. Chem.* **1989**, *12*, 437-446.
(166) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev. (Washington, D. C.)* **2000**, *100*, 3257-3282.
(167) Makabe, H.; Negishi, E.-I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., Ed; John Wiley & Sons: NY, 2002; Vol 1, pp 2789-2823.
(168) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853-887.
(169) Benechie, M.; Skrydstrup, T.; Khuong-Huu, F. *Tetrahedron Lett.* **1991**, *32*, 7535.
(170) Marshall, J. A.; Yanik, M. M.; Adams, N. D.; Ellis, K. C.; Chobanian, H. R. *Organic Syntheses* **2005**, *81*, 157-170.
(171) The majority of the work on the chloroynediene synthesis was performed by Jessica M. Smith and Olukorede Agusto.

(172) Li, Y.; Lu, B.; Li, C.; Li, Y. *Synth. Commun.* **2003**, *33*, 1417-1423.

(173) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769-3772.

(174) Kurti, L.; Czako, B. *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Burlington, MA, 2005.

(175) Qian, M.; Negishi, E. *Org. Process Res. Dev.* **2003**, *7*, 412-417.

(176) A large portion of the work on the triflylynediene synthesis was performed by Jessica M. Smith.

(177) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683-684.

(178) Negishi, E.; Bagheri, V.; Chatterjee, S.; Luo, F. T.; Miller, J. A.; Stoll, A. T. *Tetrahedron Lett.* **1983**, *24*, 5181-5184.

(179) Reginato, G.; Mordini, A.; Degl'Innocenti, A.; Caracciolo, M. *Tetrahedron Lett.* **1995**, *36*, 8275-8278.

(180) Hanack, M.; Sproesser, L. *J. Am. Chem. Soc.* **1978**, *100*, 7066-7068.

(181) Hanack, M. *Acc. Chem. Res.* **1976**, *9*, 364-371.

(182) Jackel, K.-P.; Hanack, M. *Tetrahedron Lett.* **1974**, *17*, 1637-1640.

(183) Stang, P. J.; Fisk, T. E. *Synthesis* **1979**, 438-440.

(184) Stang, P. J.; Ladika, M. *Synthesis* **1981**, 29-30.

(185) Jacobsen, E. N.; Bergman, R. G. *J. Am. Chem. Soc.* **1985**, *107*, 2023-2032.

(186) Khemiss, A. *Journal De La Societe Chimique De Tunisie* **1994**, *3*, 435-443.

(187) Kraus, G. A.; Taschner, M. J. *J. Am. Chem. Soc.* **1980**, *102*, 1974-7.

(188) Masquelin, T.; Obrecht, D. *Synthesis* **1995**, 276-84.

(189) Botvinnik, E. V.; Blandov, A. N.; Kuznetsov, M. A. *Russ. J. Org. Chem.* **2001**, *37*, 421-425.

(190) Metler, T.; Uchida, A.; Miller, S. I. *Tetrahedron* **1968**, *24*, 4285-97.

(191) Marson Charles, M.; Edaan, E.; Morrell James, M.; Coles Simon, J.; Hursthouse Michael, B.; Davies David, T. *Chem Commun (Cambridge, U.K.)* **2007**, 2494-6.

(192) Marson, C. M.; Edaan, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. *Abstracts of Papers,* 232nd ACS National Meeting, San Francisco, CA, United States, Sept. 10-14, 2006; American Chemical Society: Washington, DC, 2006; ORGN-309.

(193) Wadsworth, D. H.; Geer, S. M.; Detty, M. R. *J. Org. Chem.* **1987**, *52*, 3662-3668.

(194) Detty, M. R.; McGarry, L. W. *J. Org. Chem.* **1988**, *53*, 1203-1207.

(195) Detty, M. R.; Virkler, P. R. Production of Dye Intermediates and Polymethine Dyes Therefrom. WO 2002000642, 2002.

(196) Marei, M. G. *J. Chem. Soc. Pak.* **1992**, *14*, 121-125.

(197) Marei, M. G.; El-Ghanam, M. *Indian J. Chem., Sect. B* **1993**, *32B*, 318-321.

(198) Parker, W.; Raphael, R. A.; Wilkinson, D. I. *J. Chem. Soc.* **1958**, 3871-3875.

(199) Rosiak, A.; Christoffers, J. *Tetrahedron Lett.* **2006**, *47*, 5095-5097.

(200) Rosiak, A.; Mueller, R. M.; Christoffers, J. *Monatsh. Chem.* **2007**, *138*, 13-26.

(201) Herradura, P. S., I. The Nicholas reaction in natural product synthesis: syntheses of the paraconic acids, and (+)- and (-)-blastmycinone. II. Studies of the single electron transfer-catalyzed cyclization of enynones to prostacyclin. Ph.D. Thesis, Wesleyan University, 1999.

(202) Jacobi, P. A.; Kravitz, J. I.; Zheng, W. *J. Org. Chem.* **1995**, *60*, 376-385.

(203) Jacobi, P. A.; Brielmann, H. L.; Cann, R. O. *J. Org. Chem.* **1994**, *59*, 5305-5316.

(204) Jacobi, P. A.; Armacost, L. M.; Brielmann, H. L.; Cann, R. O.; Kravitz, J. I.; Martinelli, M. J. *J. Org. Chem.* **1994**, *59*, 5292-5304.

(205) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J. *Tetrahedron Lett.* **1988**, *29*, 6869-6872.

(206) Jacobi, P. A.; Armacost, L. M.; Kravitz, J. I.; Martinelli, M. J.; Selnick, H. G. *Tetrahedron Lett.* **1988**, *29*, 6865-6868.

(207) Koller, M.; Karpf, M.; Dreiding, A. S. *Helv. Chim. Acta* **1986**, *69*, 560-579.

(208) Koller, M.; Karpf, M.; Dreiding, A. S. *Tetrahedron Lett.* **1986**, *27*, 19-22.

(209) Jacobi, P. A.; Cann, R. O.; Skibbie, D. F. *Tetrahedron Lett.* **1992**, *33*, 2265-2268.

(210) Jacobi, P. A.; Kravitz, J. I. *Tetrahedron Lett.* **1988**, *29*, 6873-6876.

(211) Yoshida, K.; Imamoto, T. *J. Am. Chem. Soc.* **2005**, *127*, 10470-10471.

(212) Spino, C.; Thibault, C.; Gingras, S. *J. Org. Chem.* **1998**, *63*, 5283-5287.

(213) Trost, B. M.; Schmidt, T. *J. Am. Chem. Soc.* **1988**, *110*, 2301-2303.

(214) Shi Shun, A. L. K.; Chernick, E. T.; Eisler, S.; Tykwinski, R. R. *J. Org. Chem.* **2003**, *68*, 1339-1347.

(215) Stark, L. M.; Pekari, K.; Sorensen, E. J. *Proc. Natl. Acad. Sci. U. S. A.* **2004**, *101*, 12064-12066.

(216) Phansavath, P.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* **1998**, *39*, 1561-1564.

(217) Iwasawa, N.; Sakurada, F.; Iwamoto, M. *Org. Lett.* **2000**, *2*, 871-873.

(218) Laurent, A.; Villalva-Servin, N. P.; Forgione, P.; Wilson, P. D.; Smil, D. V.; Fallis, A. G. *Can. J. Chem.* **2004**, *82*, 215-226.

(219) Chouraqui, G.; Petit, M.; Phansavath, P.; Aubert, C.; Malacria, M. *Eur. J. Org. Chem.* **2006**, 1413-1421.

(220) Trost, B. M.; Sharma, S.; Schmidt, T. *Tetrahedron Lett.* **1993**, *34*, 7183-7186.

(221) Mukaiyama, T.; Matsui, S.; Homma, K.; Kobayashi, S. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 2687-2690.

(222) Towers, G. H. N.; Arnason, J. T.; Wat, C. K.; Lambert, J. D. H. Controlling Weeds Using a Naturally Occurring Conjugated Polyacetylene. CA 1172460, 1984.

(223) Satoh, M.; Watanabe, M.; Kawahata, M.; Mohri, K.; Yoshida, Y.; Isobe, K.; Fujimoto, Y. *Chem. Pharm. Bull.* **2004**, *52*, 418-421.

(224) Jones, E. R. H.; Safe, S.; Thaller, V. *J. Chem. Soc. C* **1966**, 1220-1221.

(225) Takahashi, M.; Isoi, K.; Kimura, Y.; Yoshikura, M. *Yakugaku Zasshi* **1964**, *84*, 752-6.

(226) Wat, C. K.; Prasad, S. K.; Graham, E. A.; Partington, S.; Arnason, T.; Towers, G. H. N.; Lam, J. *Biochem. Syst. Ecol.* **1981**, *9*, 59-62.

(227) Towers, G. N. H.; Arnason, T.; Wat, C. K.; Graham, E. A.; Lam, J.; Mitchell, J. C. *Contact Dermatitis* **1979**, *5*, 140-144.

(228) Schulte, K. E.; Potter, B. *Arch. Pharm. (Weinheim, Ger.)* **1977**, *310*, 945-963.

(229) Schulte, K. E.; Wulfhorst, G. *Arch. Pharm. (Weinheim, Ger.)* **1977**, *310*, 285-298.

(230) Fukumaru, T.; Awata, H.; Hamma, N.; Komatsu, T. *Agric. Biol. Chem.* **1975**, *39*, 519-527.

(231) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1975**, *108*, 2541-2546.

(232) Bohlmann, F.; Miethe, R. *Chem. Ber.* **1971**, *104*, 1362-1374.

(233) Bohlmann, F.; Zdero, C. *Chem. Ber.* **1972**, *105*, 1783-1784.

(234) Bohlmann, F.; Rode, K. M. *Chem. Ber.* **1968**, *101*, 1889-1891.

(235) Bohlmann, F. *Chem. Ber.* **1967**, *100*, 3454-3456.

(236) Bohlmann, F.; Niedballa, U.; Rode, K. M. *Chem. Ber.* **1966**, *99*, 3552-3558.

(237) Bohlmann, F.; Bornowski, H.; Arndt, C. *Chem. Ber.* **1966**, *99*, 2828-2834.

(238) Bohlmann, F.; Niedballa, U.; Schneider, J. *Chem. Ber.* **1965**, *98*, 3010-3014.

(239) Bohlmann, F.; Arndt, C.; Bornowski, H.; Jastrow, H.; Kleine, K. M. *Bet.* **1962**, *95*, 1320-1327.

(240) Bohlmann, F.; Arndt, C.; Bornowski, H.; Kleine, K. M. *Bet.* **1962**, *95*, 1315-1319.

(241) Bohlmann, F.; Bornowski, H. *Chem. Ber.* **1961**, *94*, 3189-3192.

(242) Bohlmann, F.; Arndt, C.; Bornowski, H.; Kleine, K. *Chem. Ber.* **1961**, *94*, 958-967.

(243) Bohlmann, F.; Herbst, P.; Gleinig, H. *Chem. Ber.* **1961**, *94*, 948-957.

(244) Bohlmann, F.; Zdero, C.; Grenz, M. *Phytochemistry* **1976**, *15*, 1309-1310.

(245) Bohlmann, F.; Zdero, C. *Phytochemistry* **1976**, *15*, 1177.

(246) Bohlmann, F.; Zdero, C. *Phytochemistry* **1977**, *16*, 776-777.

(247) Bohlmann, F.; Zdero, C. *Phytochemistry* **1977**, *16*, 1065-1068.

(248) Christensen, L. P.; Lam, J.; Thomasen, T. *Phytochemistry* **1991**, *30*, 4151-4152.

(249) Lam, J.; Christensen, L. P.; Thomasen, T. *Phytochemistry* **1992**, *31*, 2881-2882.

(250) Lund, E. D. *Phytochemistry* **1992**, *31*, 3621-3623.

(251) Komakine, N.; Okasaka, M.; Takaishi, Y.; Kawazoe, K.; Murakami, K.; Yamada, Y. *J. Nat. Med.* **2006**, *60*, 135-137.

(252) Bohlmann, F.; Zdero, C.; Suwita, A. *Chem. Ber.* **1975**, *108*, 2818-2821.

(253) Bohlmann, F.; Zdero, C.; Grenz, M. *Chem. Ber.* **1975**, *108*, 2822-2823.

(254) Bohlmann, F.; Grenz, M. *Tetrahedron Lett.* **1970**, 1453-1456.

(255) Bohlmann, F.; Fritz, U. *Phytochemistry* **1978**, *17*, 1769-1772.

(256) Bohlmann, F.; Jakupovic, J.; Ahmed, M.; Grenz, M.; Suding, H.; Robinson, H.; King, R. M. *Phytochemistry* **1981**, *20*, 113-116.

(257) Bohlmann, F.; Wegner, P.; Jakupovic, J. *Phytochemistry* **1982**, *21*, 1109-1114.

(258) Harada, R.; Iwasaki, M. *Phytochemistry* **1982**, *21*, 2009-2011.

(259) Bohlmann, F.; Zdero, C. *Phytochemistry* **1982**, *21*, 2743-2745.

(260) Yun, H.; Chou, T.-C.; Dong, H.; Tian, Y.; Li, Y.-M.; Danishefsky, S. J. *J. Org. Chem.* **2005**, *70*, 10375-10380.

(261) Morita, M.; Hirakura, K.; Yanagisawa, T.; Mihashi, H. Isolation of Polyacetylene Compounds as 5-lipoxygenase Inhibitors. JP 01224367, 1989.

(262) Hirakura, K.; Morita, M.; Yanagisawa, T.; Mihashi, H. Polyacetylenes as 5-lipoxygenase Inhibitors for Allergy Treatment. JP 02184682, 1990.

(263) Pagani, F. *Boll. Chim. Farm.* **1981**, *120*, 213-221.

(264) Hausen, B. M.; Broehan, J.; Koenig, W. A.; Faasch, H.; Hahn, H.; Bruhn, G. *Contact Dermatitis* **1987**, *17*, 1-9.

(265) Fujimoto, Y.; Satoh, M.; Takeuchi, N.; Kirisawa, M. *Chem. Pharm. Bull.* **1991**, *39*, 521-523.

(266) Satoh, Y.; Satoh, M.; Isobe, K.; Mohri, K.; Yoshida, Y.; Fujimoto, Y. *Chem. Pharm. Bull.* **2007**, *55*, 561-564.

(267) Hu, C. Q.; Chang, J. J.; Lee, K. H. *J. Nat. Prod.* **1990**, *53*, 932-935.

(268) Kwon, B. M.; Ro, S. H.; Kim, M. K.; Nam, J. Y.; Jung, H. J.; Lee, I. R.; Kim, Y. K.; Bok, S. H. *Planta Med.* **1997**, *63*, 552-553.

(269) Gier, D. W.; Calhoon, A. M. Killing Fungi and Nematodes with Acetylenic Ketones. US 3592922, 1971.

(270) Gier, D. W.; Calhoon, A. M. Killing Fungi with Acetylenic Ketones. US 3699232, 1972.

(271) Medne, K.; Zile, A.; Glazunova, N. P.; Vereshchagin, L. I. *Latv. PSR Zinat. Akad. Vestis* **1969**, 137-140.

(272) Rele, D. N.; Baskaran, S.; Korde, S. S.; Vora, J. D.; Trivedi, G. K. *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.* **1996**, *35B*, 431-436.

(273) Wu, T. S.; Tsang, Z. J.; Wu, P. L.; Lin, F. W.; Li, C. Y.; Teng, C. M.; Lee, K. H. *Bioorg. Med. Chem.* **2001**, *9*, 77-83.

(274) Wu, T.-S.; Tsang, Z.-J.; Wu, P.-L.; Liou, M.-J.; Leu, Y.-L.; Chan, Y.-Y.; Lin, F.-W.; Shi, L.-S. *Phytochemistry* **1998**, *47*, 1645-1648.

(275) Hong, R.; Chen, Y.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 3478-3481.

(276) Baldwin, J. E.; Adlington, R. M.; Wilkinson, P. J.; Marquez, R.; Adamo, M. F. A. *Heterocycles* **2003**, *59*, 81-85.

(277) Stork, G.; Tomasz, M. *J. Am. Chem. Soc.* **1964**, *86*, 471.

(278) Yun, H.; Danishefsky, S. J. *J. Org. Chem.* **2003**, *68*, 4519-4522.

(279) Garcia, J.; Lopez, M.; Romeu, J. *Synlett* **1999**, 429-431.

(280) Evans, D. A.; Kvoerno, L.; Mulder, J. A.; Raymer, B.; Dunn, T. B.; Beauchemin, A.; Olhava, E. J.; Juhl, M.; Kagechika, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4693-4697.

(281) Parker, K. A.; Katsoulis, I. A. *Org. Lett.* **2004**, *6*, 1413-1416.

(282) Houghton, T. J.; Choi, S.; Rawal, V. H. *Org. Lett.* **2001**, *3*, 3615-3617.

(283) Wang, C.; Forsyth, C. J. *Org. Lett.* **2006**, *8*, 2997-3000.

(284) Marson, C. M.; Edaan, E.; Morrell, J. M.; Coles, S. J.; Hursthouse, M. B.; Davies, D. T. *Chem. Commun. (Cambridge, U. K.)* **2007**, 2494-2496.

(285) Toussaint, D.; Suffert, J. *Org. Synth.* **1999**, *76*, 214-220.

(286) Mladenova, M. P.; Biserkova, M. G. *Bulg. Chem. Commun.* **1999**, *31*, 98-104.

(287) Serrat, X.; Cabarrocas, G.; Rafel, S.; Ventura, M.; Linden, A.; Villalgordo, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 3417-3430.

(288) Mel'nikova, V. I.; Vasil'eva, L. L.; Pivnifsky, K. K. *Russ. Chem. Bull.* **1998**, *47*, 1199-1208.

(289) Punniyamurthy, T.; Bhatia, B.; Reddy, M. M.; Maikap, G. C.; Iqbal, J. *Tetrahedron* **1997**, *53*, 7649-7670.

(290) Kundu, N. G.; Pal, M.; Chowdhury, C. *J. Chem. Res., Synop.* **1995**, 4-5.

(291) Punniyamurthy, T.; Iqbal, J. *Tetrahedron Lett.* **1994**, *35*, 4007-4010.

(292) Kalra, S. J. S.; Punniyamurthy, T.; Iqbal, J. *Tetrahedron Lett.* **1994**, *35*, 4847-4850.

(293) Chung, C. B.; Chang, S. K.; Shim, S. C. *Bull. Korean Chem. Soc.* **1991**, *12*, 122-124.

(294) Obrecht, D. *Helv. Chim. Acta* **1989**, *72*, 447-456.

(295) Stepin, S. G.; Tishchenko, I. G. *Zh. Org. Khim.* **1986**, *22*, 1972-1975.

(296) Hirao, T.; Misu, D.; Agawa, T. *Tetrahedron Lett.* **1986**, *27*, 933-934.

(297) Suffert, J.; Toussaint, D. *J. Org. Chem.* **1995**, *60*, 3550-3553.

(298) Cahiez, G.; Laboue, B. *Tetrahedron Lett.* **1989**, *30*, 3545-3546.

(299) Babin, P.; Lapouyade, P.; Dunogues, J. *Can. J. Chem.* **1982**, *60*, 379-382.

(300) Verkruijsse, H. D.; Heus-Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289-294.

(301) Santelli, M.; El Abed, D.; Jellal, A. *J. Org. Chem.* **1986**, *51*, 1199-1206.

(302) Nightingale, D. V.; Wadsworth, F. *J. Am. Chem. Soc.* **1945**, *67*, 416-418.

(303) Katritzky, A. R.; Le, K. N. B.; Khelashvili, L.; Mohapatra, P. P. *J. Org. Chem.* **2006**, *71*, 9861-9864.

(304) de las Heras, M. A.; Molina, A.; Vaquero, J. J.; Garcia Navio, J. L.; Alvarez-Builla, J. *J. Org. Chem.* **1993**, *58*, 5862-5865.

(305) Wakamatsu, K.; Okuda, Y.; Oshima, K.; Nozaki, H. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2425-2426.

(306) Logue, M. W.; Teng, K. *J. Org. Chem.* **1982**, *47*, 2549-2553.

(307) Alonso, D. A.; Najera, C.; Pacheco, M. C. *J. Org. Chem.* **2004**, *69*, 1615-1619.

(308) Yin, J.; Wang, X.; Liang, Y.; Wu, X.; Chen, B.; Ma, Y. *Synthesis* **2004**, 331-333.

(309) Wang, J.-X.; Wei, B.; Huang, D.; Hu, Y.; Bai, L. *Synth. Commun.* **2001**, *31*, 3337-3343.

(310) Wang, J.-X.; Wei, B.; Hu, Y.; Liu, Z.; Fu, Y. *Synth. Commun.* **2001**, *31*, 3527-3532.

(311) Wang, J.-X.; Wei, B.; Hu, Y.; Liua, Z.; Kang, L. *J. Chem. Res., Synop.* **2001**, 146-147.

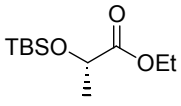
(312) Iwamoto, M.; Amaike, M. Preparation of Alkynyl Ketones. JP 03170450, 1991.

(313) Inoue, Y.; Ohuchi, K.; Imaizumi, S. *Tetrahedron Lett.* **1988**, *29*, 5941-2.
(314) Tohda, Y.; Sonogashira, K.; Hagihara, N. *Synthesis* **1977**, 777-8.
(315) Tokuyama, H.; Miyazaki, T.; Yokoshima, S.; Fukuyama, T. *Synlett* **2003**, 1512-1514.
(316) Houghton, T. J.; Choi, S.; Rawal, V. H. *Org Lett* **2001**, *3*, 3615-3617.
(317) Crisp, G. T.; Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7500-7506.
(318) Kang, S.-K.; Ho, P.-S.; Yoon, S.-K.; Lee, J.-C.; Lee, K.-J. *Synthesis* **1998**, 823-825.
(319) Kang, S.-K.; Yamaguchi, T.; Hong, R.-K.; Kim, T.-H.; Pyung, S.-J. *Tetrahedron* **1997**, *53*, 3027-3034.
(320) Pena, M. A.; Sestelo, J. P.; Sarandeses, L. A. *Synthesis* **2003**, 780-784.
(321) Kang, S. K.; Lim, K. H.; Ho, P. S.; Kim, W. Y. *Synthesis* **1997**, 874-876.
(322) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716-4721.
(323) Kobayashi, T.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* **1981**, 333-334.
(324) Agency of Industrial Sciences and Technology, Japan. Acetylenic Ketone. JP 57072921, 1982.
(325) Ciattini, P. G.; Morera, E.; Ortar, G. *Tetrahedron Lett.* **1991**, *32*, 6449-6452.
(326) Ochiai, M.; Sumi, K.; Takaoka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095-4112.
(327) Moriarty, R. M.; Kosmeder, J. W.; Zhdankin, V. V. *Encyclopedia of Reagents for Organic Synthesis*; Wiley: Chichester, 2004.
(328) Koser, G. F. *Adv. Heterocyclic Chem.* **2004**, *86*, 225-292.
(329) Varvoglis, A. *Hypervalent Iodine in Organic Synthesis*; Academic Press: London, 1997.
(330) Wipf, P. *Synthesis* **1993**, 537-557.
(331) Cenac, N.; Zablocka, M.; Igau, A.; Commenges, G.; Majoral, J.-P.; Skowronska, A. *Organometallics* **1996**, *15*, 1208-1217.
(332) Kawanami, Y.; Katsuki, I.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5131-5132.
(333) Guo, C.; Lu, X. *J. Chem. Soc., Perkin Trans. 1* **1993**, 1921-1923.
(334) Guo, C.; Lu, X. *Tetrahedron Lett.* **1991**, *32*, 7549-7552.
(335) Hankovszky, H. O.; Hideg, K.; Lex, L.; Kulcsar, G.; Halasz, H. A. *Can. J. Chem.* **1982**, *60*, 1432-1438.
(336) Skornyakov, Y. V.; Lozinskaya, N. A.; Proskurnina, M. V.; Zefirov, N. S. *Russ. J. Org. Chem.* **2005**, *41*, 617.
(337) Ranu, B. C.; Jana, R. *J. Org. Chem.* **2005**, *70*, 8621-8624.
(338) Coutrot, P.; Grison, C.; Lachgar, M.; Ghribi, A. *Bull. Soc. Chim. Fr.* **1995**, *132*, 925-942.
(339) Hambrecht, J.; Mueller, E. *Justus Liebigs Ann. Chem.* **1977**, 387-399.
(340) Hambrecht, J.; Straub, H. *Tetrahedron Lett.* **1976**, 1079-1082.
(341) Tamaru, Y.; Kimura, M. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley & Sons: New York, 2002; Vol. 1, pp 2425-2454.

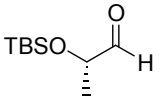
(342) Boeckman, R. K., Jr.; Ramaiah, M. *J. Org. Chem.* **1977**, *42*, 1581-1586.
(343) Corey, E. J.; Beames, D. J. *J. Amer. Chem. Soc.* **1972**, *94*, 7210-7211.
(344) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*; John Wiley & Sons, Inc., 2002; Vol. 1, pp 273-280.
(345) Hollingworth, G. J.; Sweeney, J. B. *Synlett* **1993**, 463-465.
(346) Tanaka, H.; Yamada, H.; Matsuda, A.; Takahashi, T. *Synlett* **1997**, 381-383.
(347) Clive, D. L. J.; Tao, Y.; Bo, Y.; Hu, Y.-Z.; Selvakumar, N.; Sun, S.; Daigneault, S.; Wu, Y.-J. *Chem. Commun. (Cambridge, U.K.)* **2000**, 1341-1350.
(348) Timbart, L.; Cintrat, J.-C. *Chem.--Eur. J.* **2002**, *8*, 1637-1640.
(349) Xiong, Z.-C.; Huang, X. *J. Chem. Res., Synop.* **2003**, 372-373.
(350) Huang, X.; Xiong, Z.-C. *Synth. Commun.* **2003**, *33*, 2511-2517.
(351) Guanti, G.; Riva, R. *Org. Biomol. Chem.* **2003**, *1*, 3967-3976.
(352) Sorg, A.; Siegel, K.; Brueckner, R. *Chem.--Eur. J.* **2005**, *11*, 1610-1624.
(353) Lipshutz, B. H.; Clososki, G. C.; Chrisman, W.; Chung, D. W.; Ball, D. B.; Howell, J. *Org. Lett.* **2005**, *7*, 4561-4564.
(354) Cai, M. Z.; Zhao, H. *Chin. Chem. Lett.* **2004**, *15*, 1157-1160.
(355) Kim, S.; Kim, S.; Lee, T.; Ko, H.; Kim, D. *Org. Lett.* **2004**, *6*, 3601-3604.
(356) Banfi, L.; Basso, A.; Gandolfo, V.; Guanti, G.; Riva, R. *Tetrahedron Lett.* **2004**, *45*, 4221-4223.
(357) Magriotis, P. A.; Scott, M. E.; Kim, K. D. *Tetrahedron Lett.* **1991**, *32*, 6085-6088.
(358) Zapata, A. J.; Rondon, A. C. *Main Group Met. Chem.* **1997**, *20*, 27-30.
(359) Suzenet, F.; Parrain, J.-L.; Quintard, J.-P. *Eur. J. Org. Chem.* **1999**, 2957-2963.
(360) Yoshida, H.; Shirakawa, E.; Kurahashi, T.; Nakao, Y.; Hiyama, T. *Organometallics* **2000**, *19*, 5671-5678.
(361) Shirakawa, E.; Nakao, Y.; Tsuchimoto, T.; Hiyama, T. *Chem. Commun. (Cambridge, U. K.)* **2002**, 1962-1963.
(362) Baxter, P. N. W. *Chem.--Eur. J.* **2003**, *9*, 5011-5022.
(363) Liu, P.-H.; Li, L.; Webb, J. A.; Zhang, Y.; Goroff, N. S. *Org. Lett.* **2004**, *6*, 2081-2083.
(364) Nakao, Y.; Shirakawa, E.; Tsuchimoto, T.; Hiyama, T. *J. Organomet. Chem.* **2004**, *689*, 3701-3721.
(365) Nakao, Y.; Tsuchimoto, T.; Shirakawa, E.; Hiyama, T. *Trans. Mater. Res. Soc. Jpn.* **2004**, *29*, 93-96.
(366) Yoshida, H.; Shirakawa, E.; Nakao, Y.; Honda, Y.; Hiyama, T. *Bull. Chem. Soc. Jpn.* **2001**, *74*, 637-647.
(367) Ma, Y.; Huang, X. *Synth. Commun.* **1997**, *27*, 3441-3447.
(368) Liebeskind, L. S.; Fengl, R. W. *J. Org. Chem.* **1990**, *55*, 5359-5364.
(369) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905-5911.
(370) Guanti, G.; Riva, R. *Chem. Commun. (Cambridge, U.K.)* **2000**, 1171-1172.
(371) Moss, D. K.; Spence, J. D.; Nantz, M. H. *J. Org. Chem.* **1999**, *64*, 4339-4343.

(372) Kang, S.-K.; Kim, W.-Y.; Jiao, X. *Synthesis* **1998**, 1252-1254.
(373) Mee, S. P. H.; Lee, V.; Baldwin, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 1132-1136.
(374) Rim, C.; Son, D. Y. *Org. Lett.* **2003**, *5*, 3443-3445.
(375) Villeneuve, K.; Jordan, R. W.; Tam, W. *Synlett* **2003**, *14*, 2123-2128.
(376) Approximately half of the crude product was chromatographed.
(377) Since roughly half the crude material was chromatographed, the true isolated yield is considerably higher.
(378) Yield determined by GC-MS.

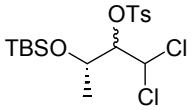
Appendix I: Compound Index



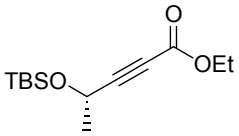
71



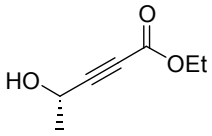
72



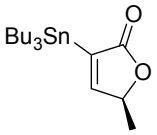
87



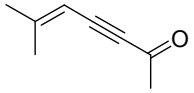
108



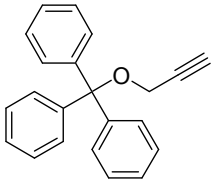
38



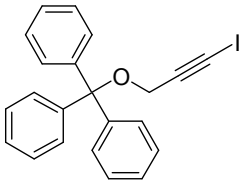
68



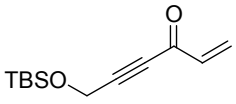
127



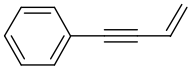
263



264

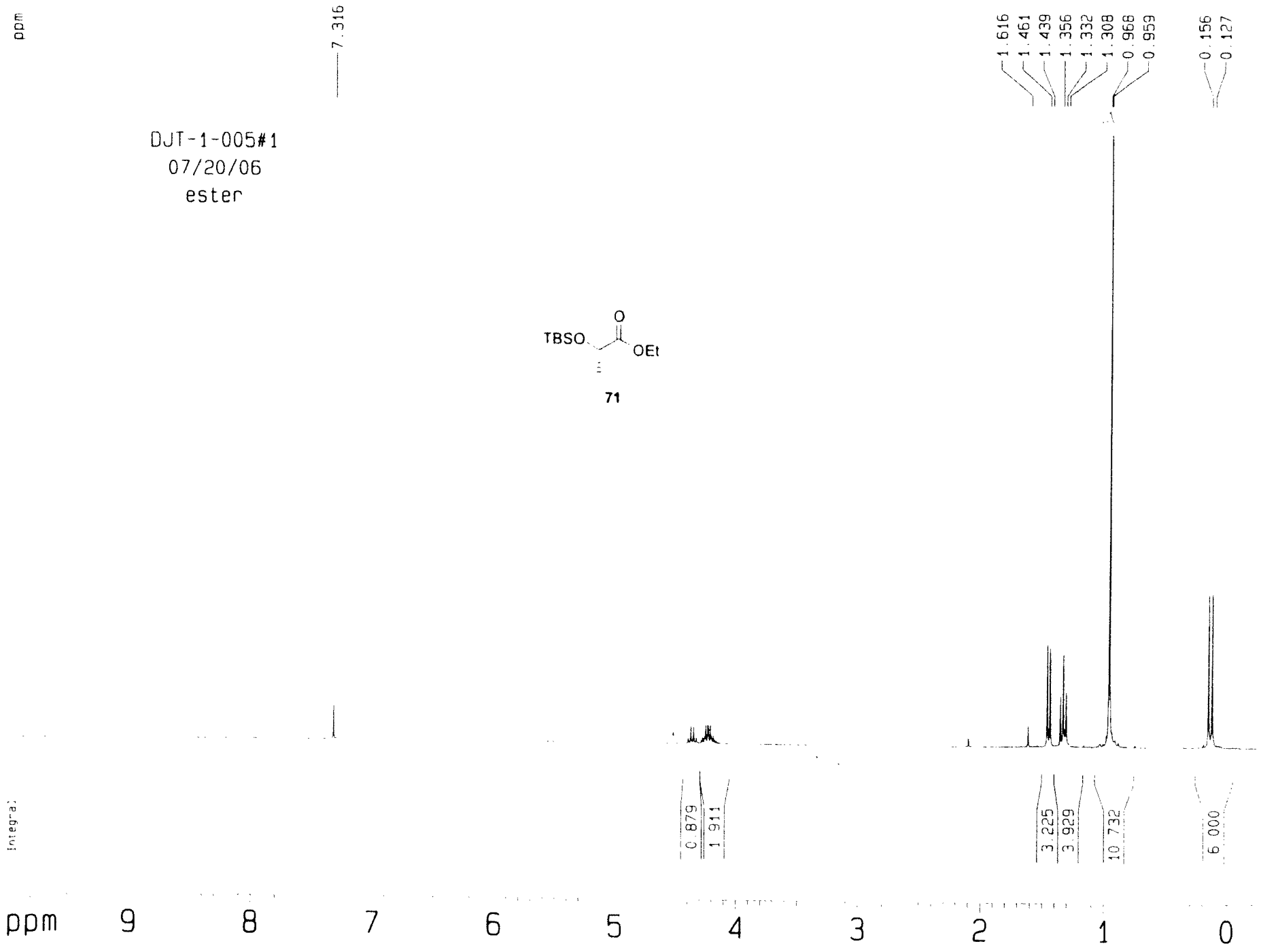


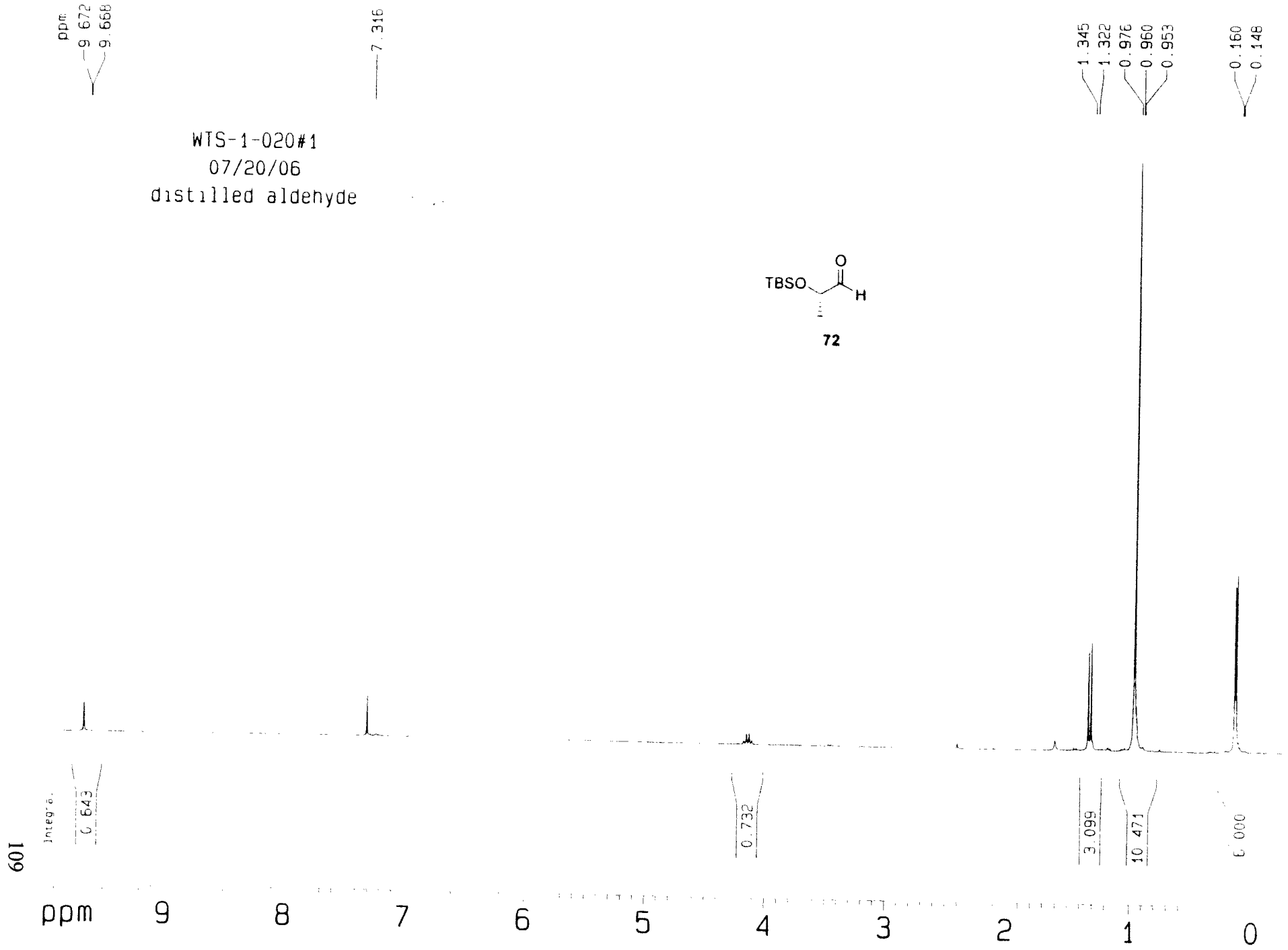
249

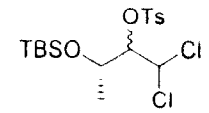


257

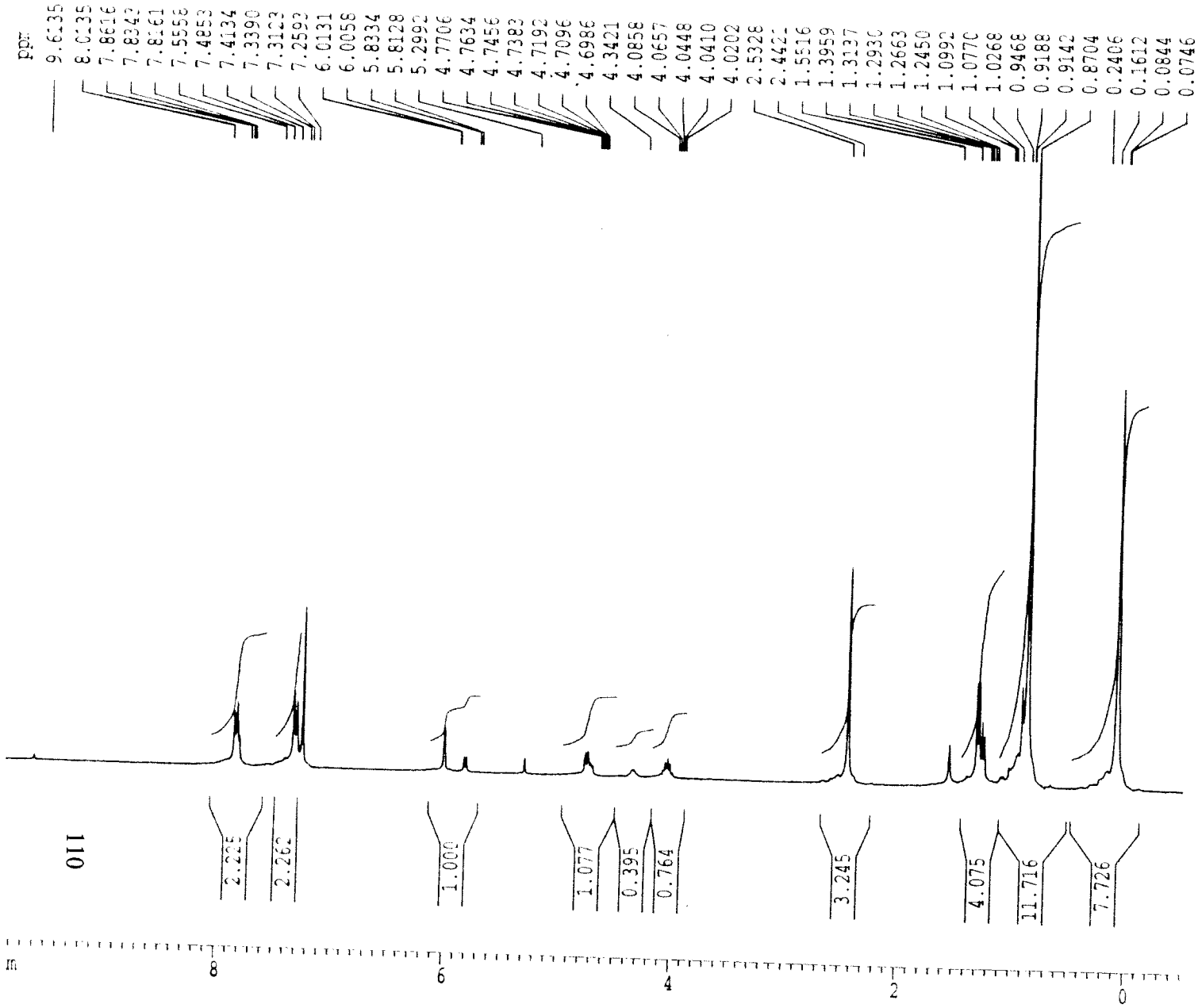
Appendix II: ^{1}H NMR, ^{13}C NMR, IR, and Mass Spectra


ppm
7.316
1.616
1.461
1.439
1.356
1.332
1.308
0.968
0.959
0.156
0.127
DJT-1-005#1
07/20/06
ester
TBSO
O
OEt
71
Integral
0.879
1.911
3.225
3.929
10.732
6.000
ppm 9 8 7 6 5 4 3 2 1 0


ppm
9.672
9.668
7.316
WTS-1-020#1
07/20/06
distilled aldehyde
TBSO
O
H
72
1.345
1.322
0.976
0.960
0.953
0.160
0.148
Integral
0.643
0.732
3.099
10.471
6.000
ppm
9
8
7
6
5
4
3
2
1
0



87



110

Current Data Parameters

NAME	wts-1-104#5
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20070608
Time	19.40
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	512
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

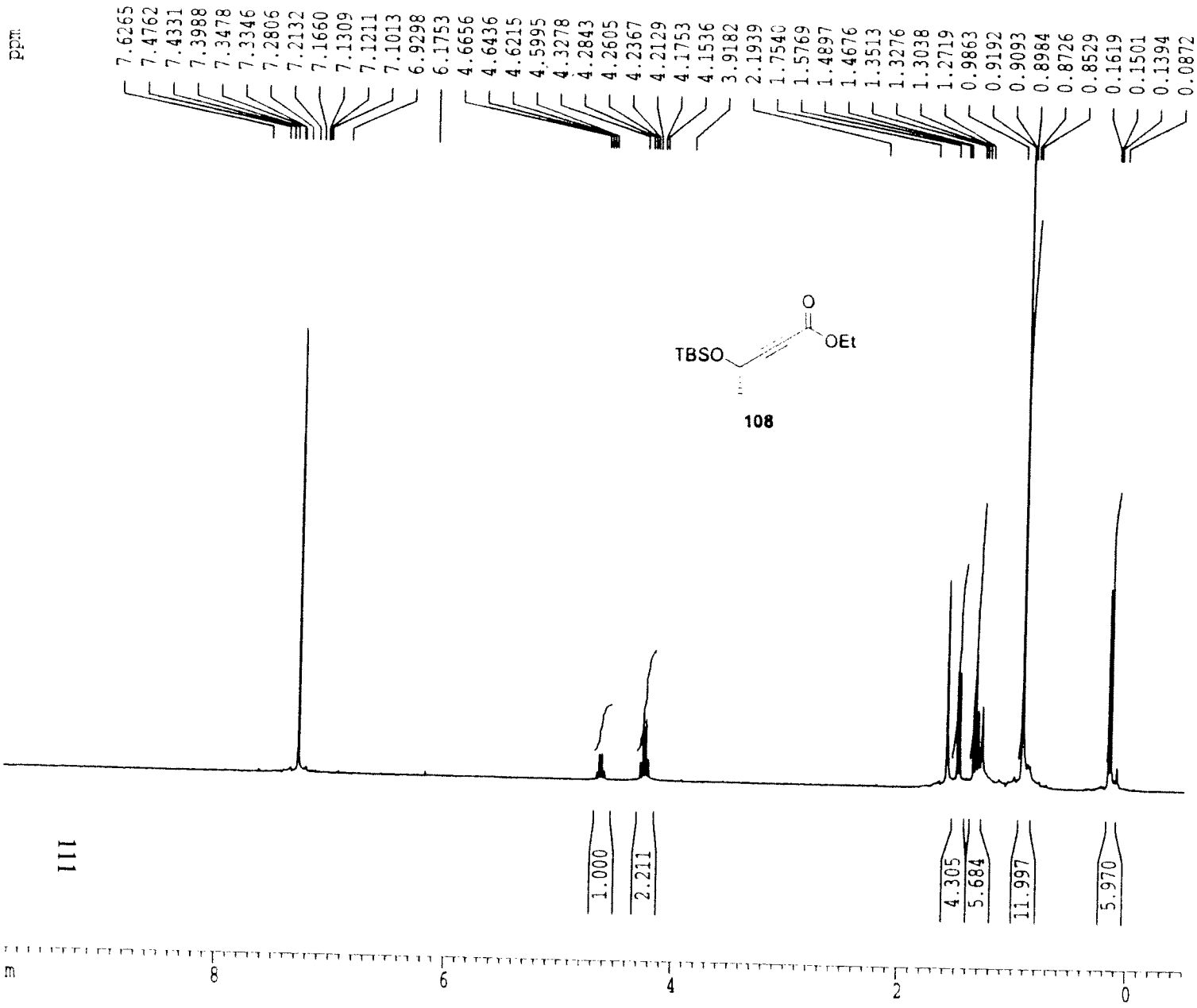
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300064 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm



111

Current Data Parameters

NAME	WTS-1-040H
EXPNO	9
PROCNO	1

F2 - Acquisition Parameters

Date_	20060817
Time	16.47
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	912.3
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

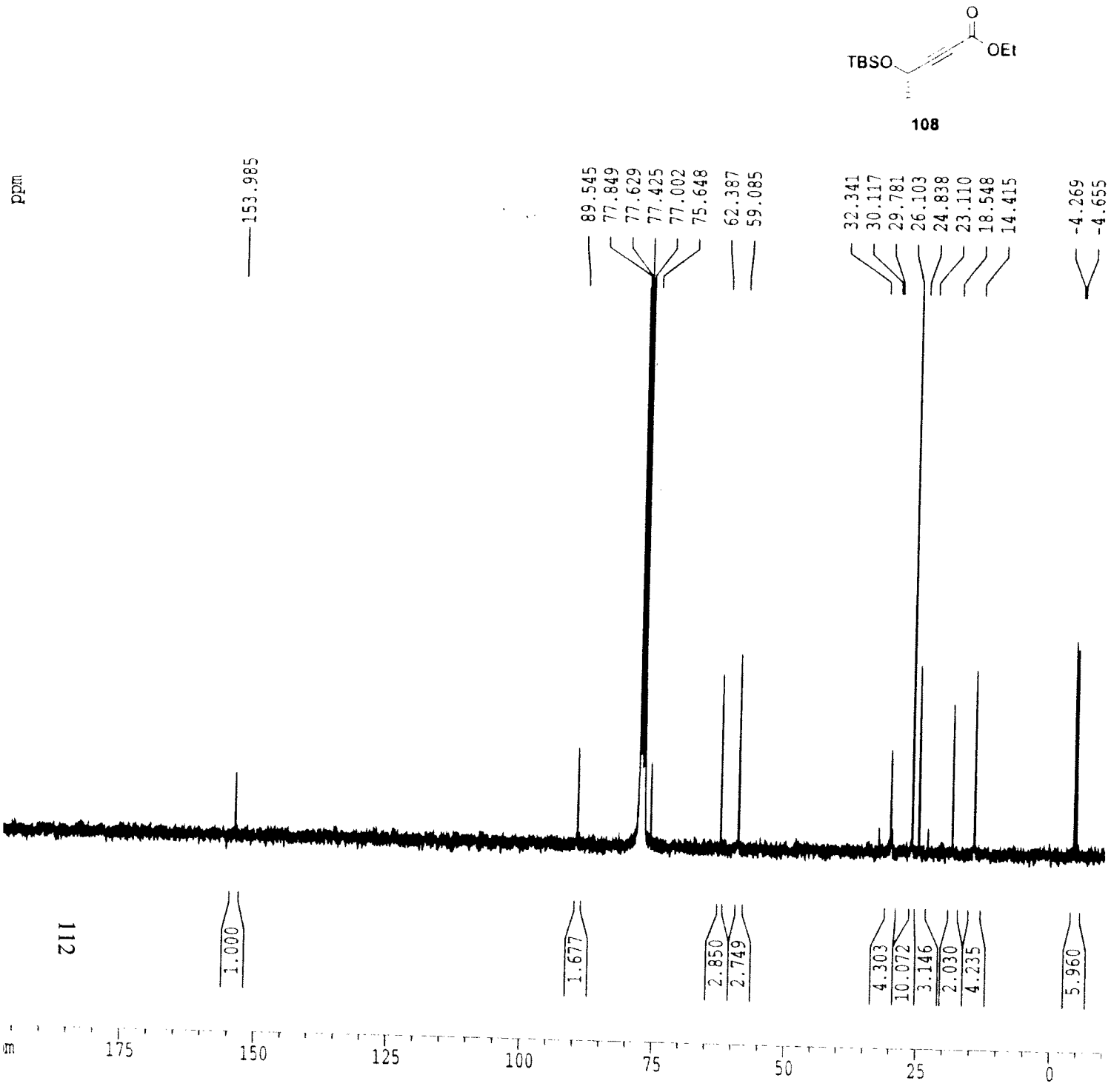
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm



112

Current Data Parameters

NAME	WTS-1-040C3
EXPNO	9
PROCNO	1

F2 - Acquisition Parameters

Date_	20060825
Time	9.13
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zgpg30
TD	65536
SOLVENT	CDCl3
NS	19200
DS	2
SWH	18832.393 Hz
FIDRES	0.287360 Hz
AQ	1.7400308 sec
RG	8192
DW	26.550 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec
D11	0.03000000 sec
D12	0.00002000 sec

========== CHANNEL f1 ==========

NUC1	13C
P1	8.20 usec
PL1	0.00 dB
SFO1	75.4760200 MHz

========== CHANNEL f2 ==========

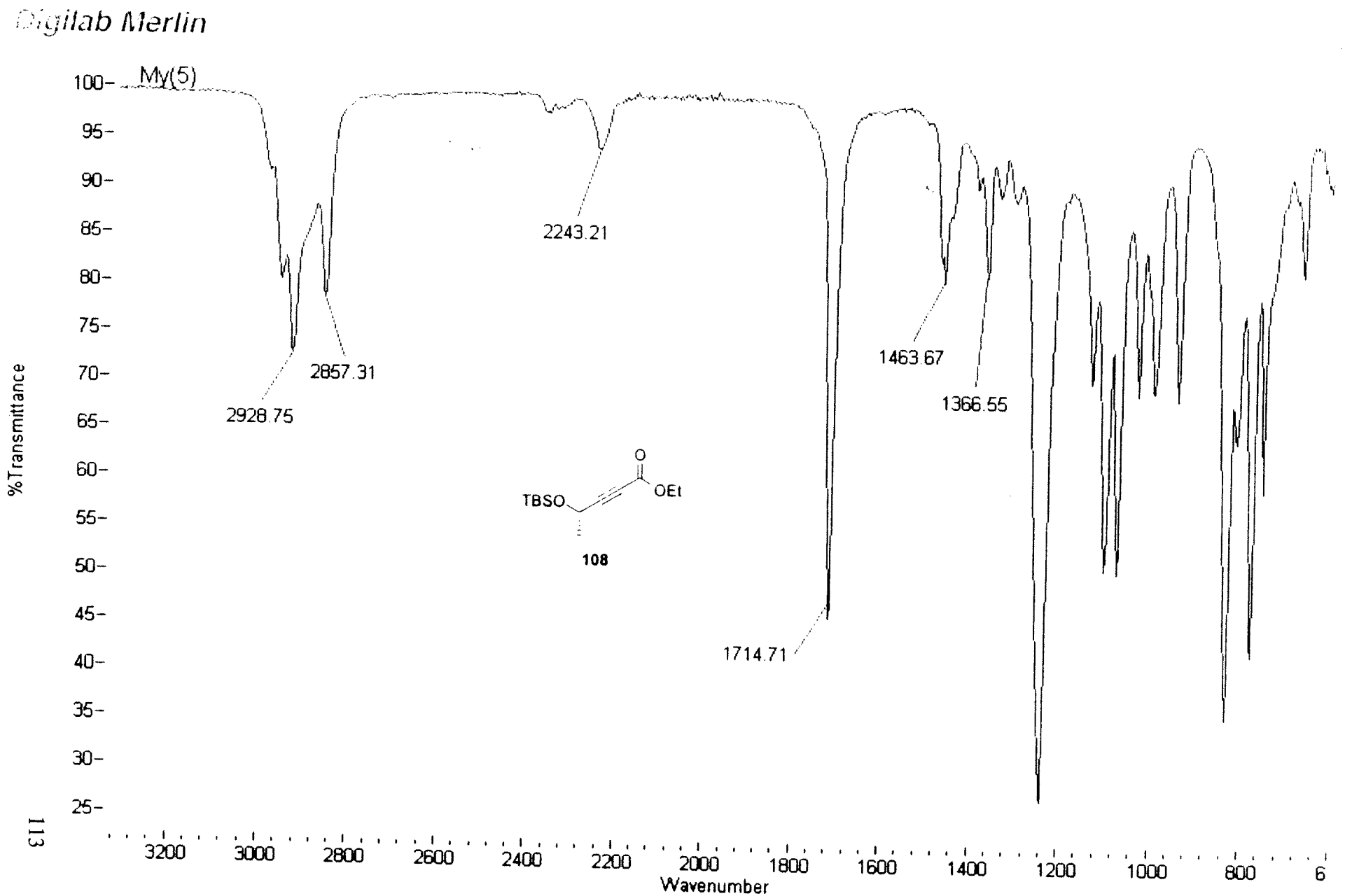
CPDPRG2	waltz16
NUC2	1H
PCPD2	100.00 usec
PL2	0.00 dB
PL12	19.00 dB
PL13	35.00 dB
SFO2	300.1312005 MHz

F2 - Processing parameters

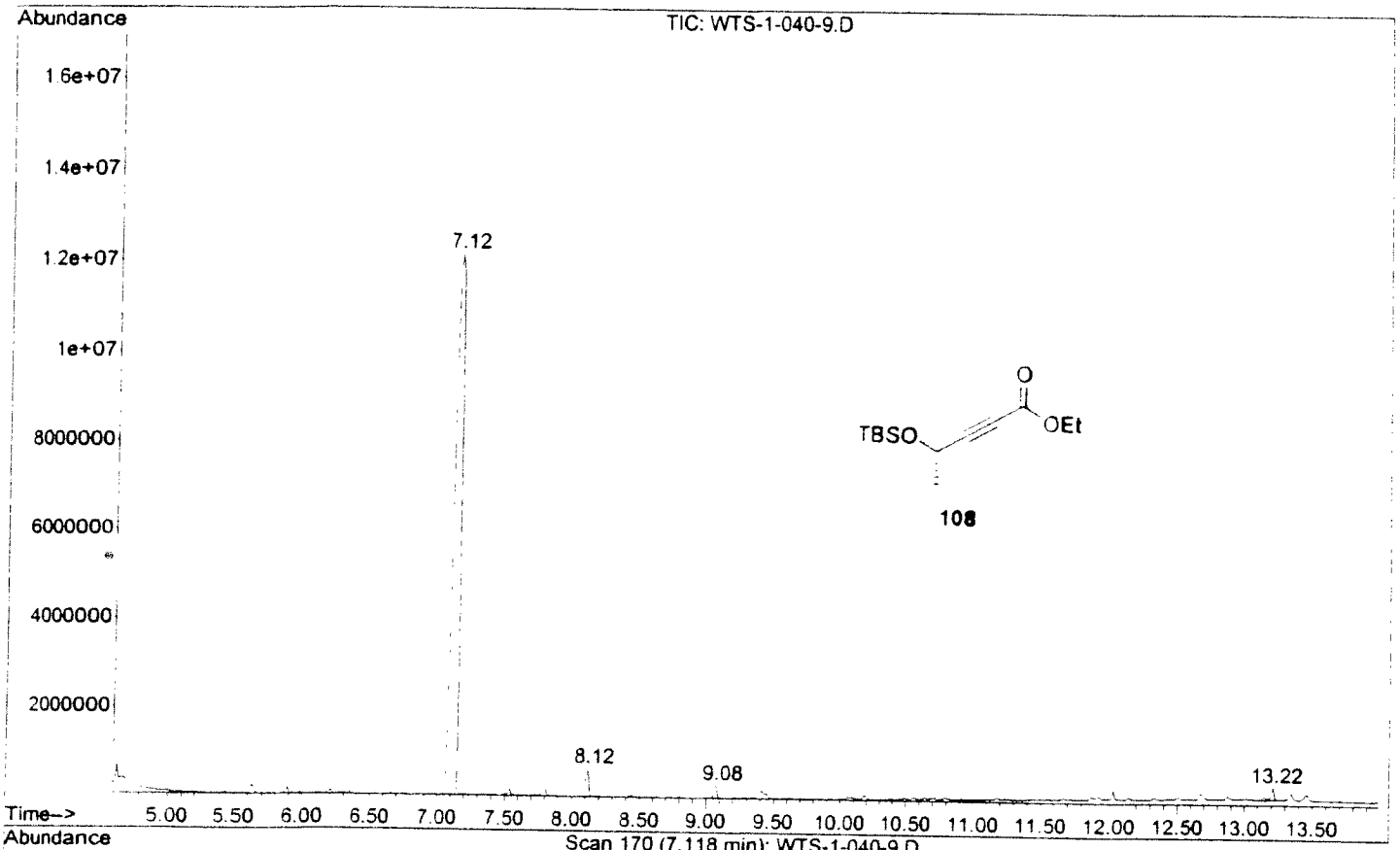
SI	32768
SF	75.4677190 MHz
WDW	EM
SSB	0
LB	1.00 Hz
GB	0
PC	1.40

1D NMR plot parameters

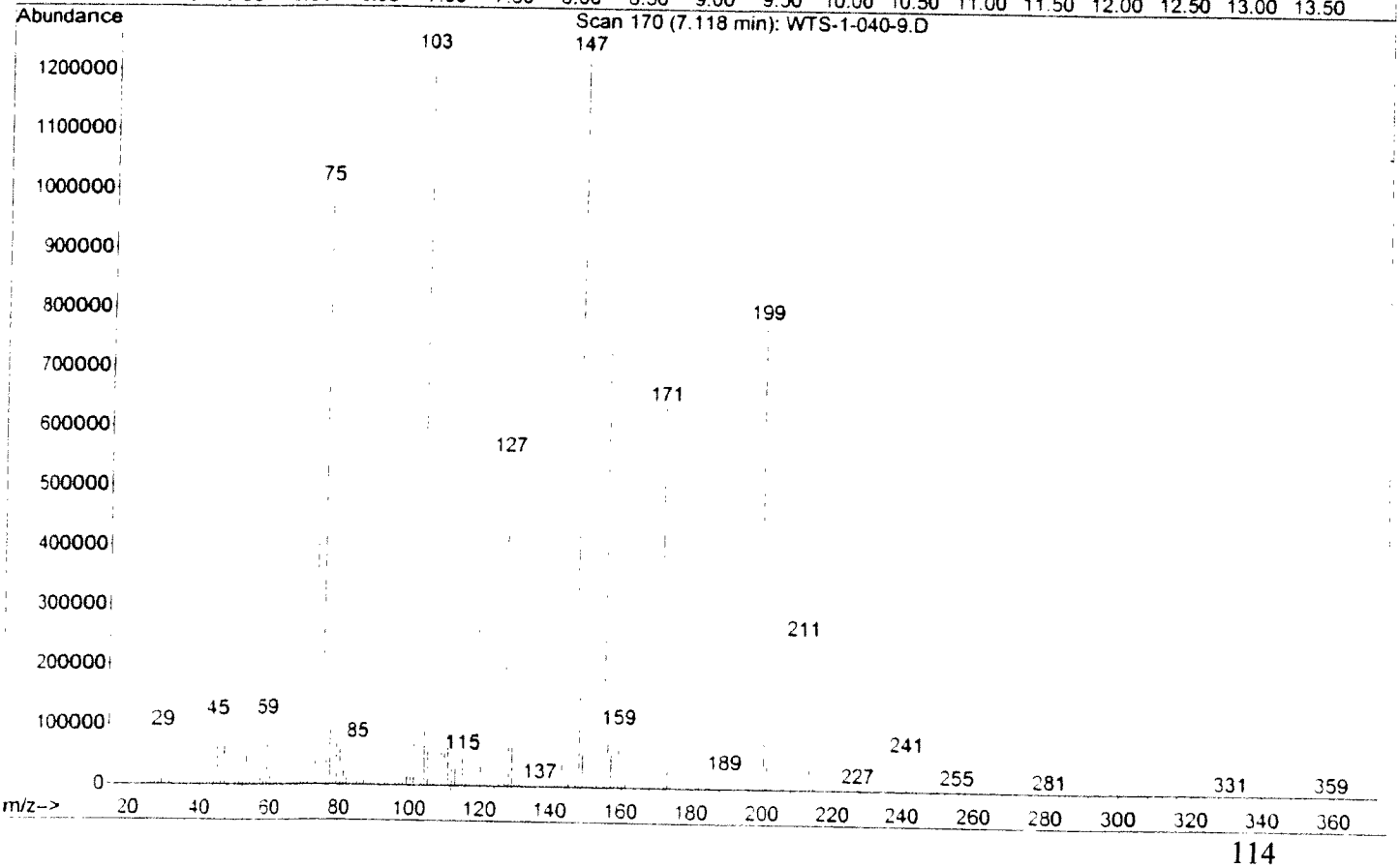
CX	20.00 cm
F1P	200.000 ppm
F1	15093.54 Hz
F2P	-10.000 ppm
F2	-754.68 Hz
PPMCM	10.50000 ppm/cm
HZCM	792.41101 Hz/cm

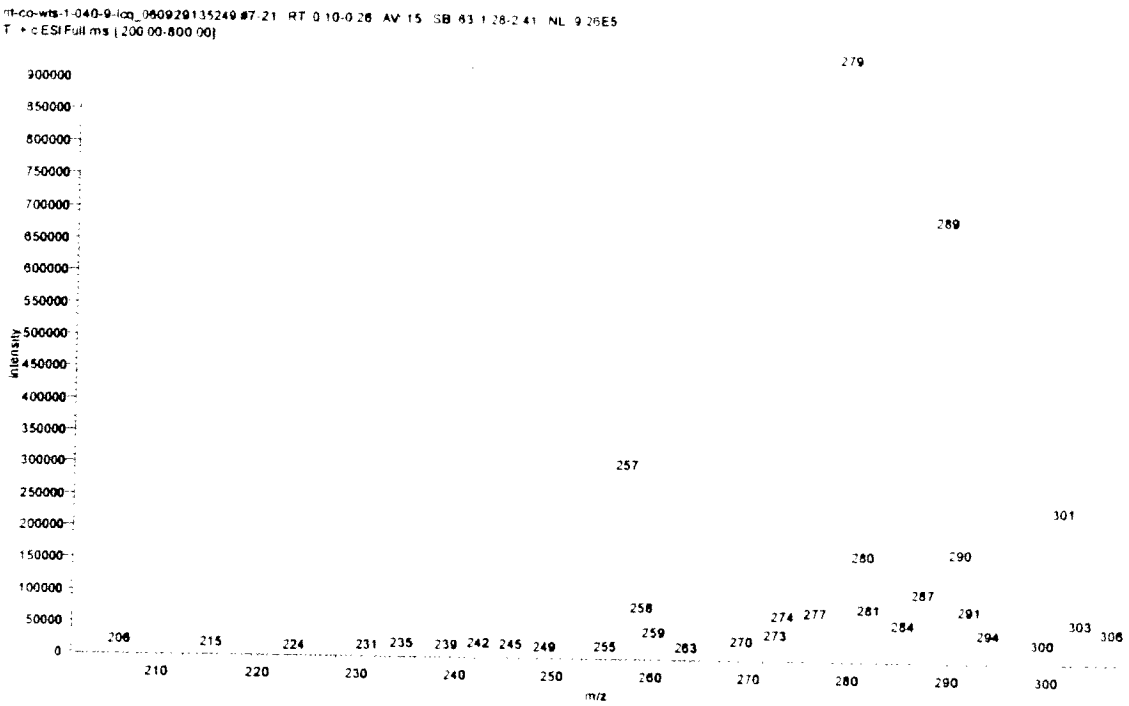

Digilab Merlin
My(5)
100-
95-
90-
85-
80-
75-
70-
65-
60-
55-
50-
45-
40-
35-
30-
25-
%Transmittance
2928.75
2857.31
2243.21
1714.71
1463.67
1366.55
TBSO
O
OEt
108
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
6
Wavenumber

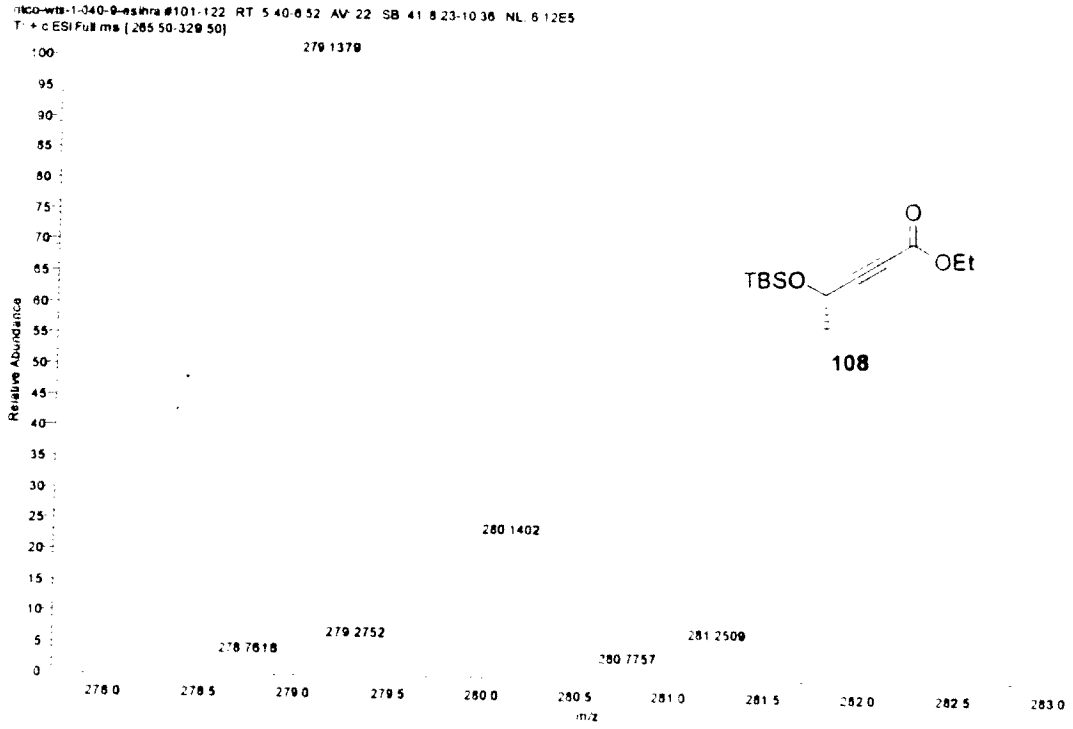
File :C:\MSDChem\1\DATA\WTS-1-040-9.D
Operator : wts
Acquired : 17 Aug 2006 11:13 using AcqMethod CGCGROUP.M
Instrument : GCMS
Sample Name: WTS-1-040-9
Misc Info : alkynoate
Vial Number: 1



108



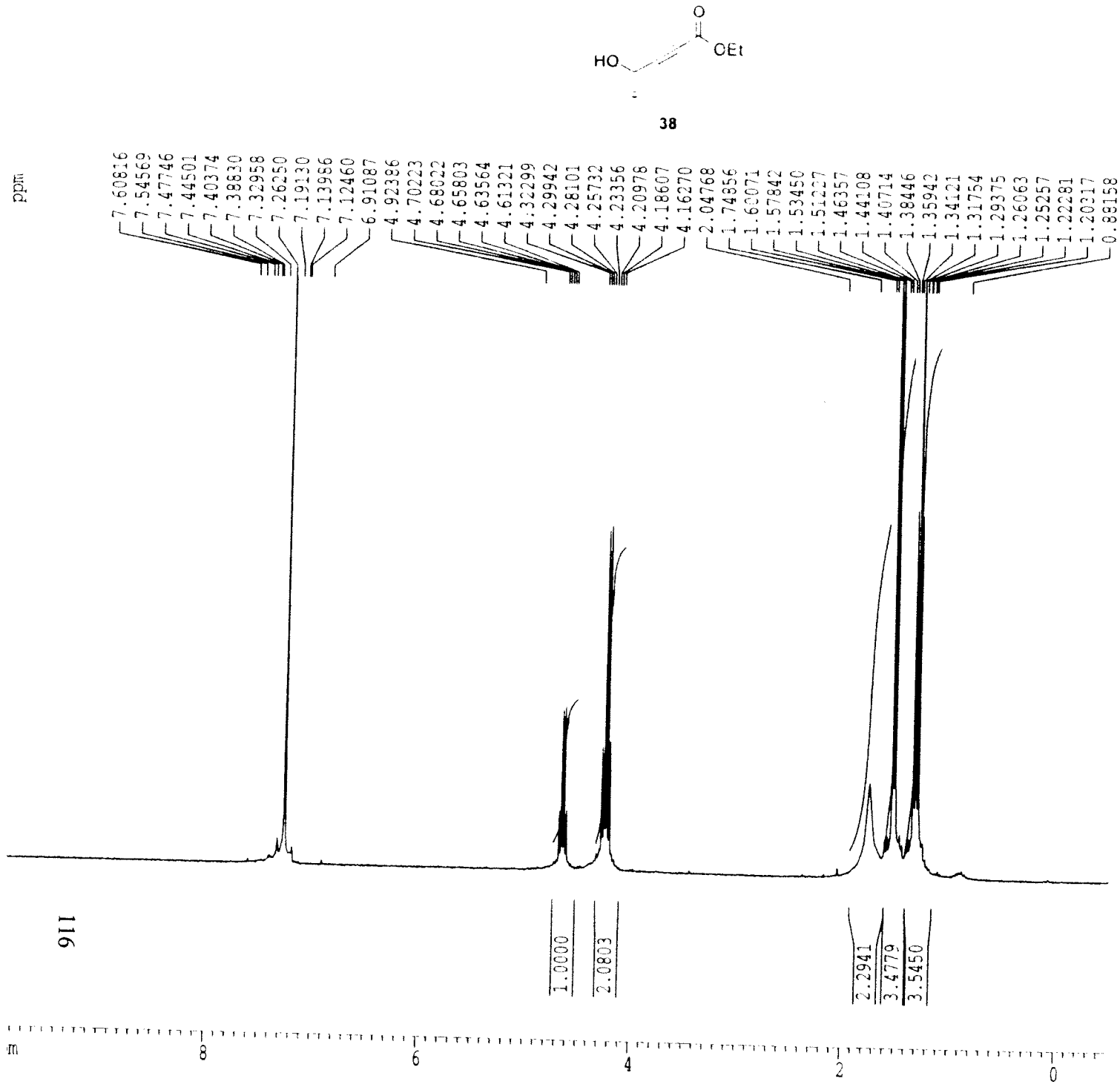




108

SPECTRUM - List: Clipboard Mode

Mass	Relative Intensity	Theoretical Mass	Delta [ppm]	Delta [mmu]	RDB	Composition
279.13791	100.0	279.1380	-0.2	-0.0	10.5	<<C19 H19 O2 >>



Current Data Parameters

NAME	WTS 1 090f129
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20070426
Time	16.04
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	64
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	912.3
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

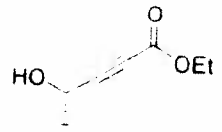
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

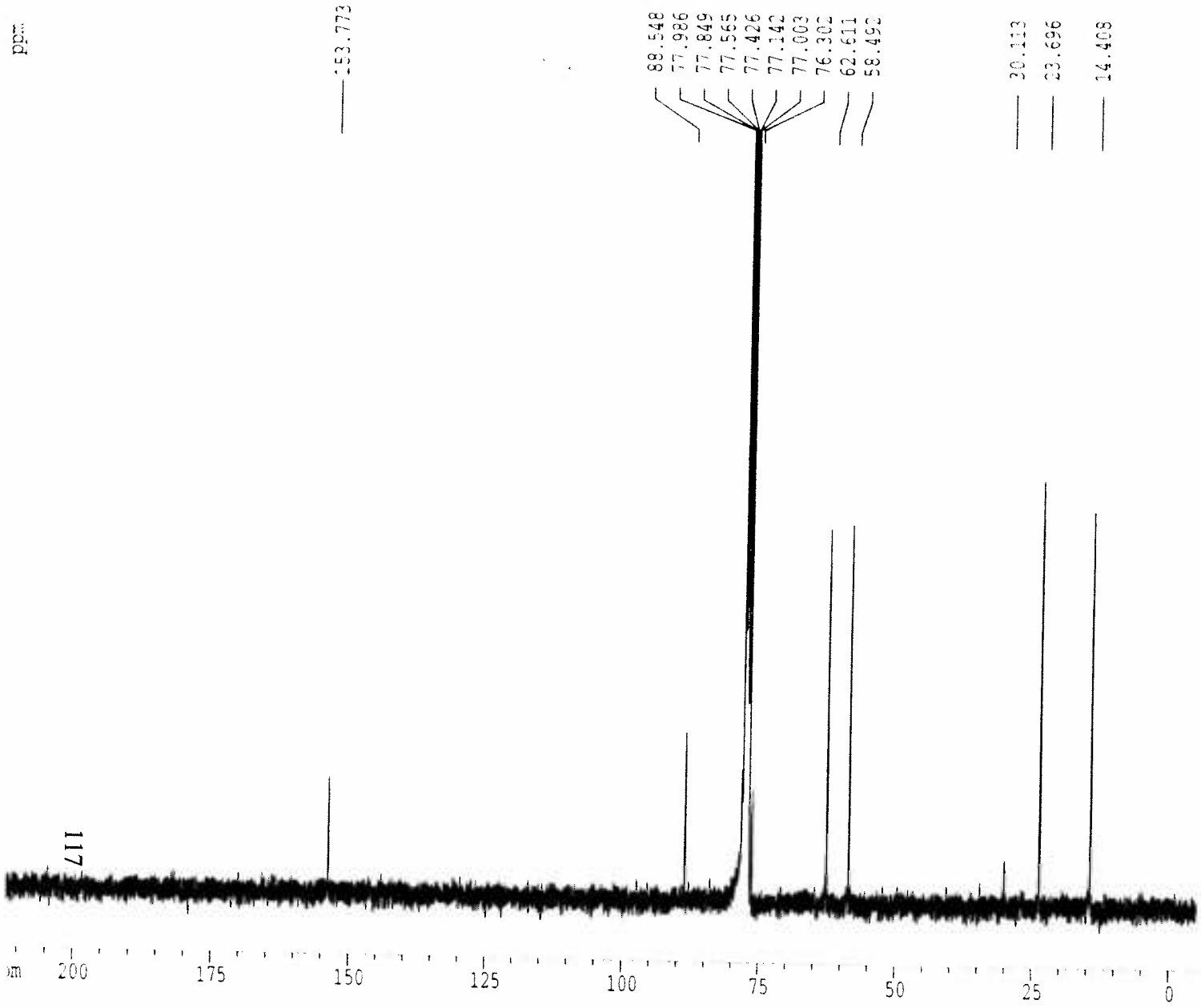
SI	32768
SF	300.1300058 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

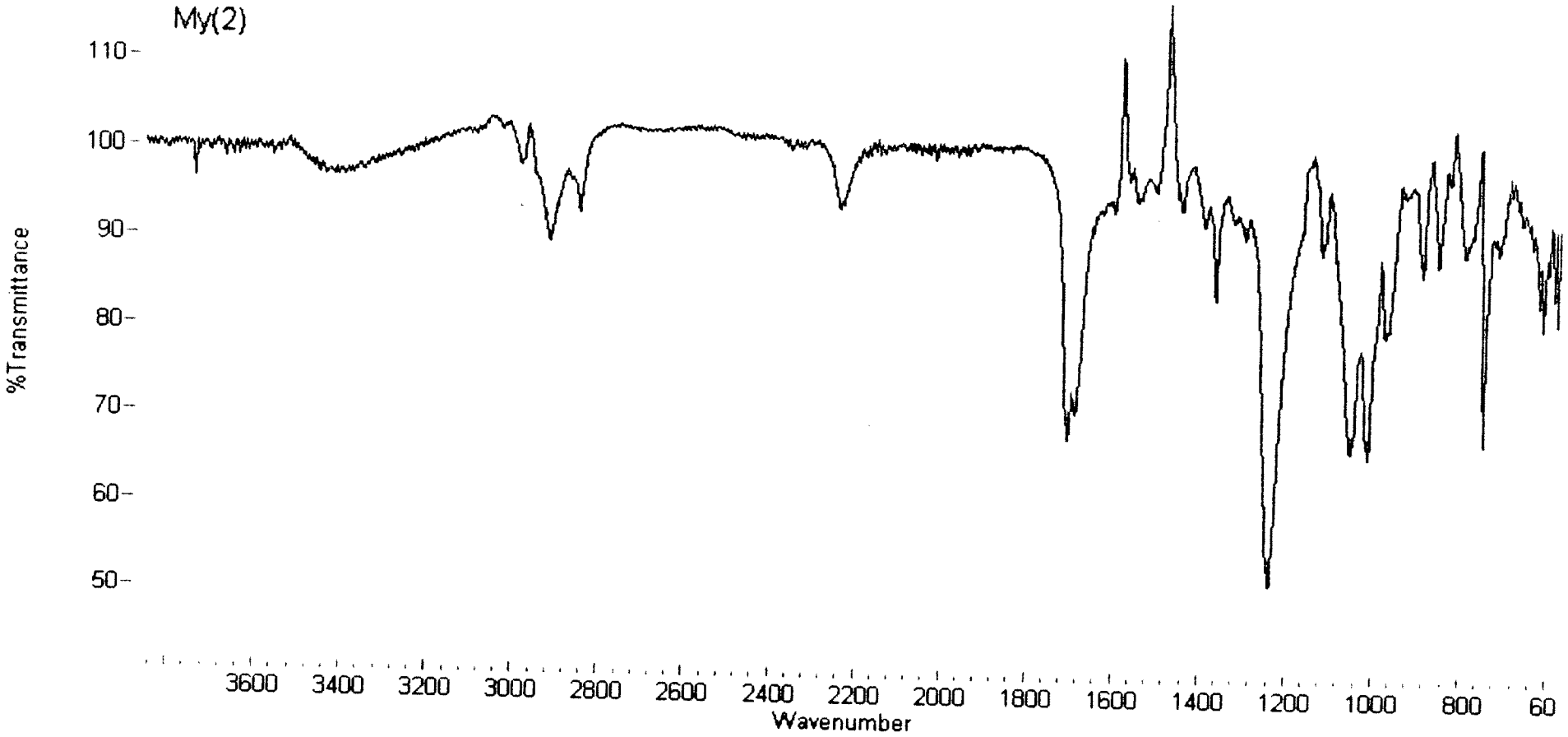


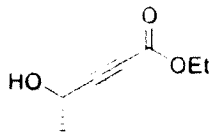
38



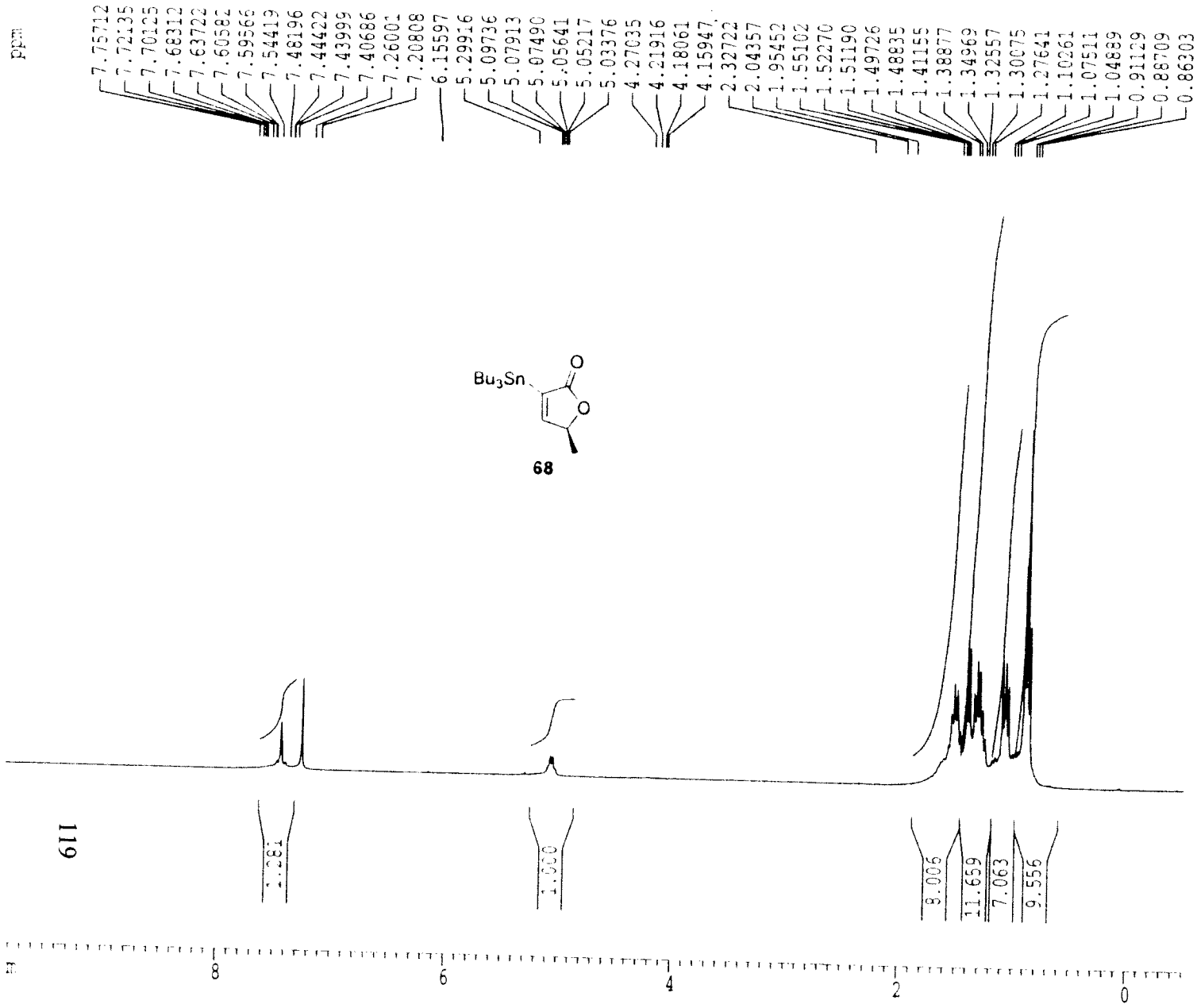

```
Current Data Parameters
NAME        WTS1053#4c13
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080423
Time                5.51
INSTRUM             spect
PROBHD     5 mm CNP  1H
PULPROG             zgpg30
TD                  65536
SOLVENT             CDCl3
NS                  10000
DS                      2
SWH           18832.393 Hz
FIDRES        0.287360 Hz
AQ            1.7400309 sec
RG                   2048
DW              26.550 usec
DE               6.00 usec
TE              300.0 K
D1            1.00000000 sec
D11           0.03000000 sec
D12           0.00002000 sec

============ CHANNEL f1 ============
NUC1                13C
P1                8.20 usec
PL1               0.00 dB
SFO1         75.4760290 MHz

============ CHANNEL f2 ============
CPDPRG2         waltz16
NUC2                1H
PCPD2           100.00 usec
PL2               0.00 dB
PL12             19.00 dB
PL13             35.00 dB
SFO2         300.1312005 MHz

F2 - Processing parameters
SI                  32768
SF           75.4677190 MHz
WDW                    EM
SSB                     0
LB                   1.00 Hz
GB                      0
PC                   1.40

1D NMR plot parameters
CX                  20.00 cm
F1P               215.000 ppm
F1              16225.56 Hz
F2P                -5.000 ppm
F2               -377.34 Hz
PPMCM            11.00000 ppm/cm
HZCM           830.14489 Hz/cm
```

Digilab Merlin





38



Current Data Parameters

NAME	WTS-1-094#2nso
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20070504
Time	15.00
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	256
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

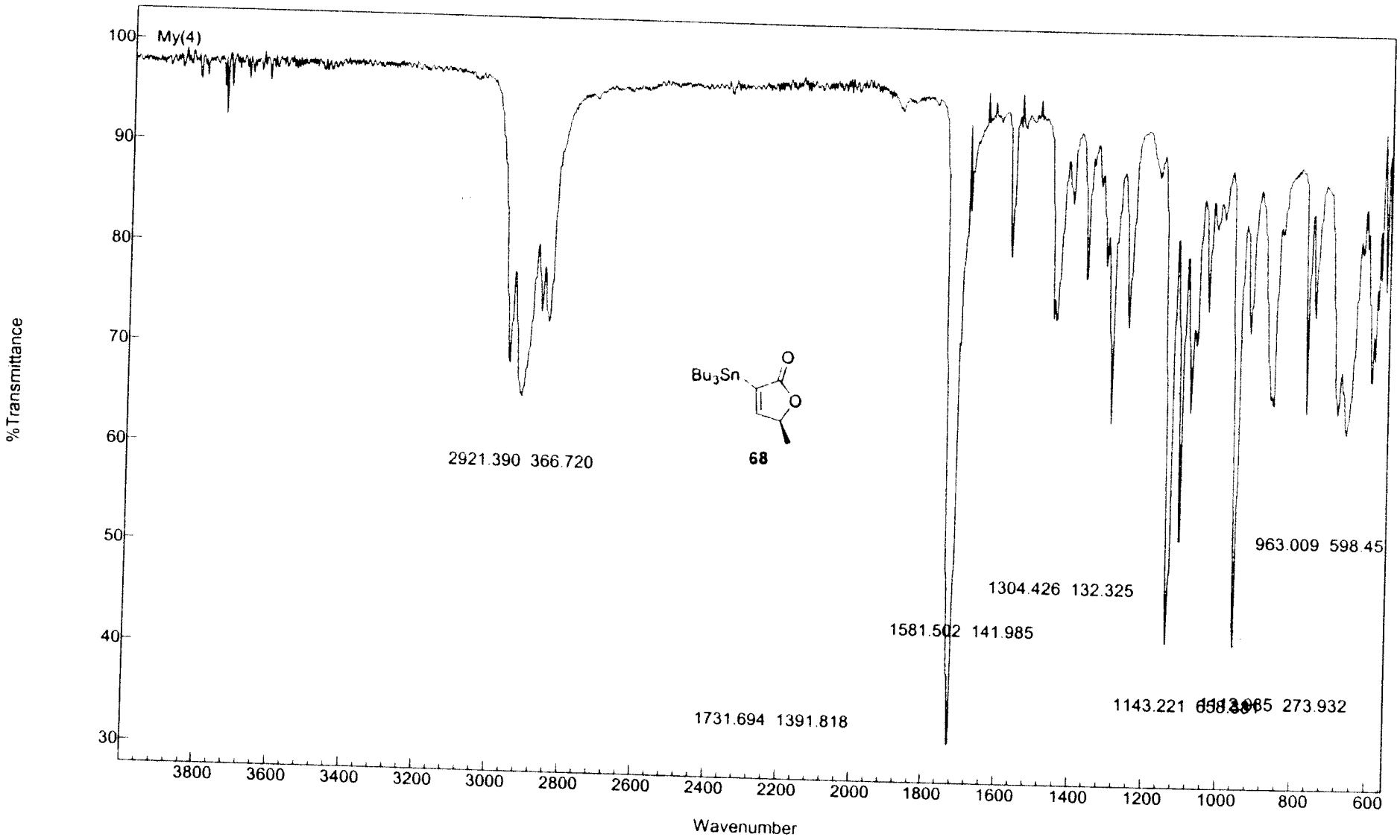
F2 - Processing parameters

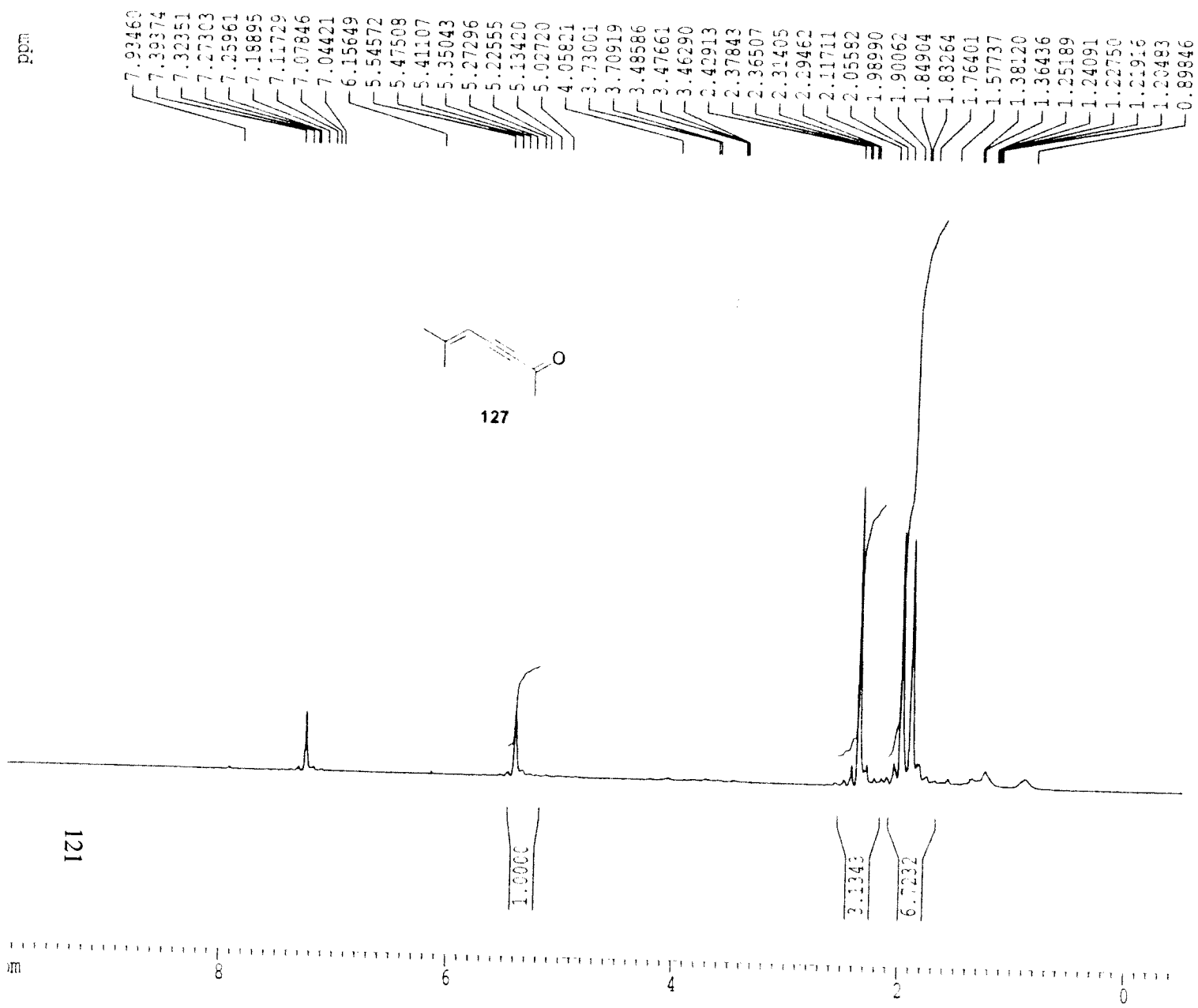
SI	32768
SF	300.1300058 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

wts-1-102#2


My(4)
% Transmittance
100
90
80
70
60
50
40
30
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
Wavenumber
2921.390 366.720
1731.694 1391.818
1581.502 141.985
1304.426 132.325
1143.221
963.009 598.45
273.932
Bu3Sn
O
O
68



Current Data Parameters

NAME	wts-3-031#2r2
EXPNO	20
PROCNO	1

F2 - Acquisition Parameters

Date_	20080218
Time	16.29
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	574.7
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

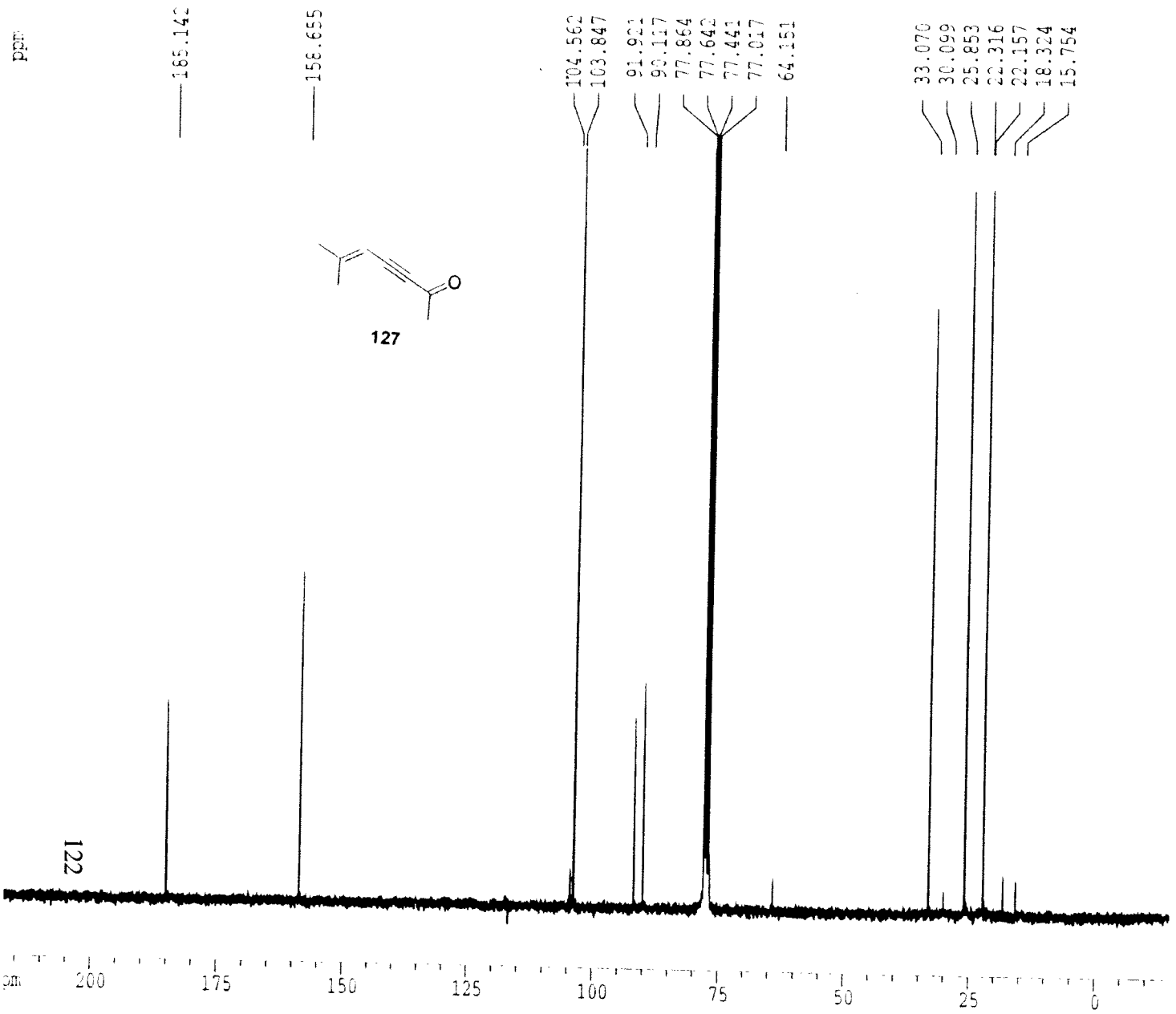
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

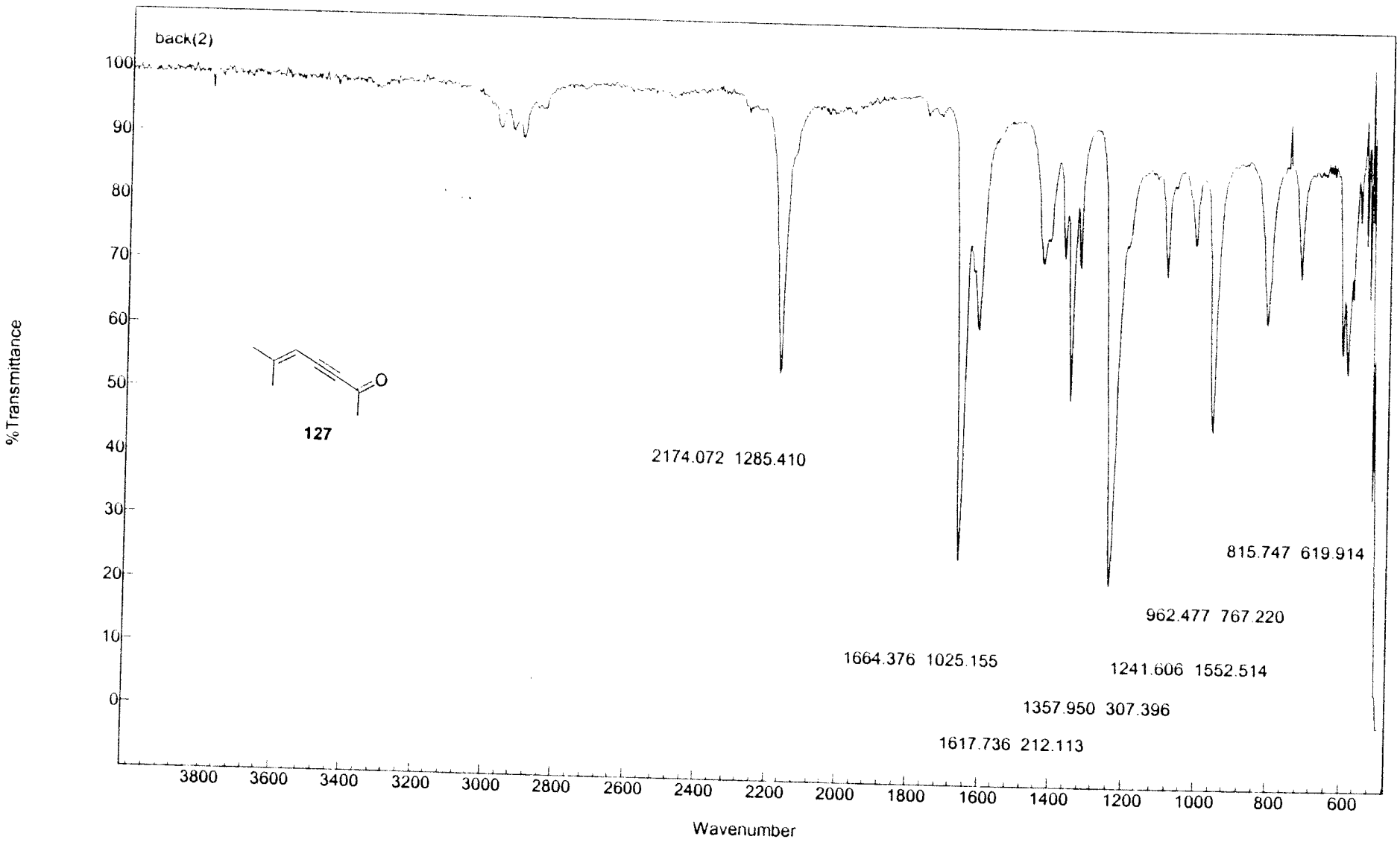
SI	32768
SF	300.1300056 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

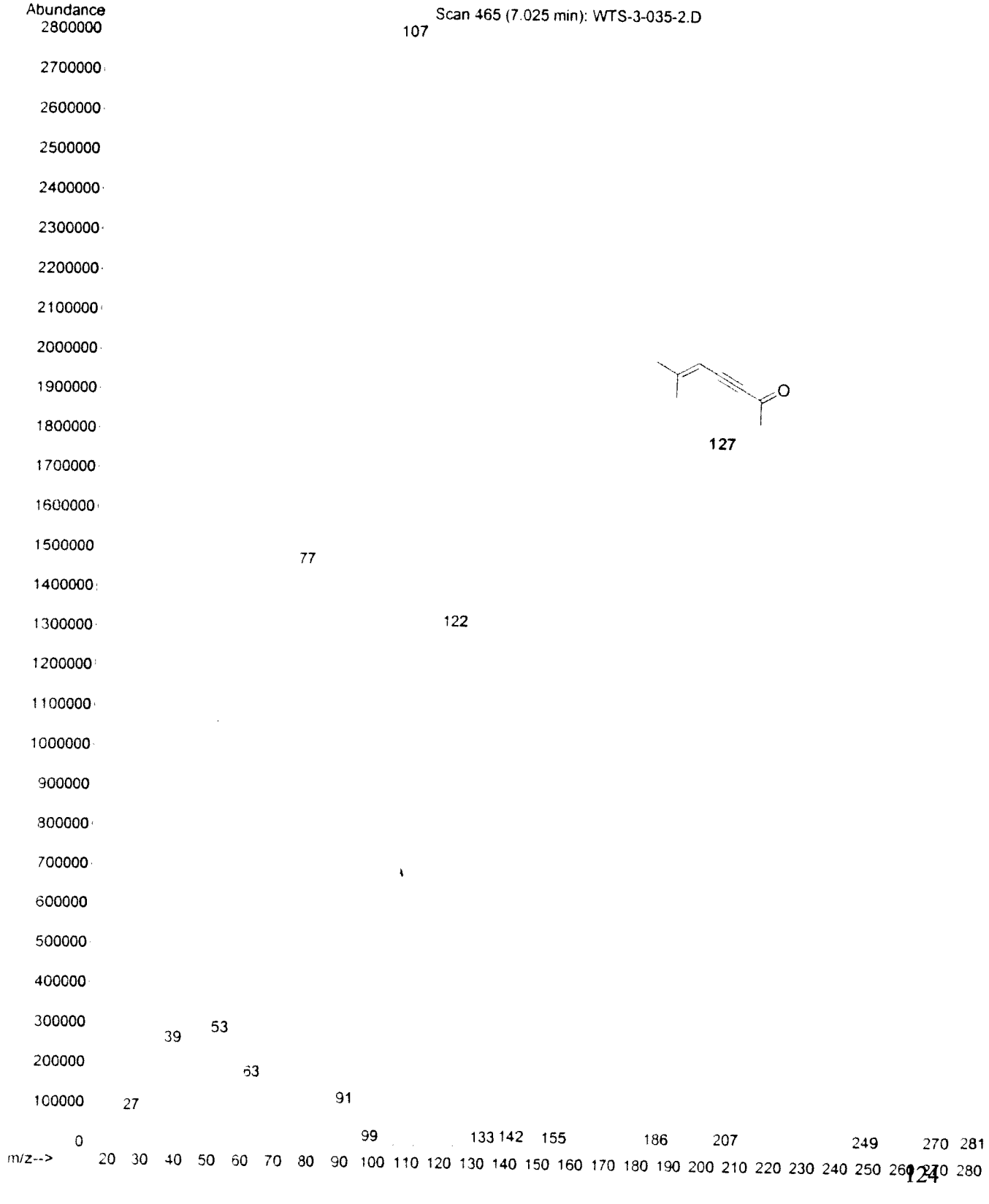
CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

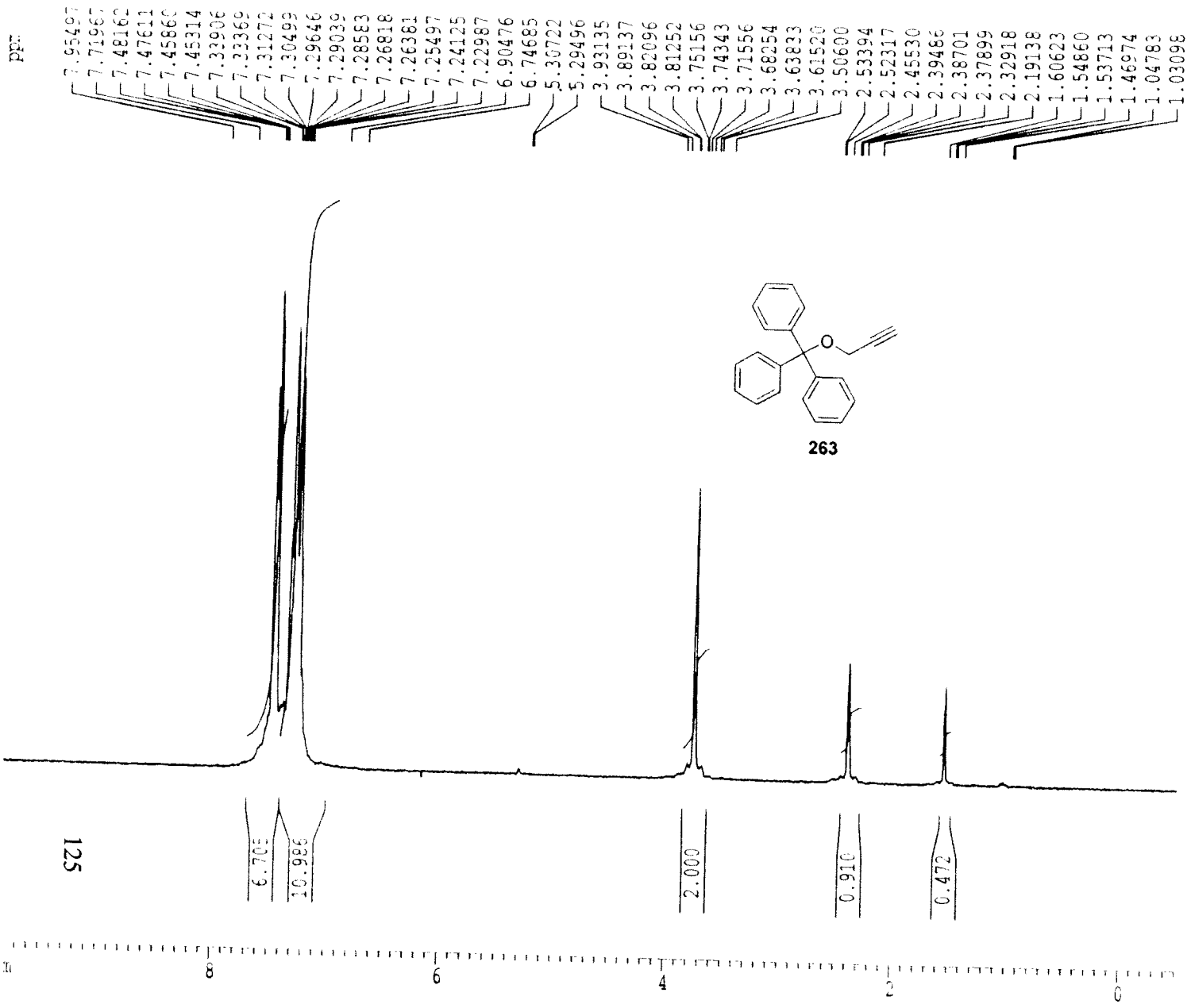



```
Current Data Parameters
NAME      wts-s 035-2c13
EXPNO                 20
PROCNO                 1

F2 - Acquisition Parameters
Date_           20080319
Time                5.34
INSTRUM            spect
PROBHD     5 mm QNP  1H
PULPROG          zgpg30
TD                65536
SOLVENT           CDCl3
NS                17096
DS                    2
SWH          [illegible] Hz
FIDRES       0.[illegible] Hz
AQ           1.74000368 sec
RG                 4096
DW               26.550 usec
DE                 6.00 usec
TE                300.0 K
D1           1.00000000 sec
D11          0.03000000 sec
D12          0.00002000 sec

[illegible] CHANNEL f1 [illegible]
NUC1                1H
P1                8.20 usec
PL1               0.60 dB
SFO1        75.4760203 MHz

[illegible] CHANNEL f2 [illegible]
CPDPRG2         waltz16
NUC2                1H
PCPD2          [illegible] usec
PL2               0.60 dB
PL11             19.00 dB
PL13             95.00 dB
SFO2        300.1312005 MHz

F1 - Processing parameters
SI                32768
SF          75.4[illegible] MHz
WDW                EM
SSB                 0
LB                1.00 Hz
GB                  0
PC                1.40

1D NMR plot parameters
CX                20.00 cm
F1P             220.000 ppm
F1            16602.90 Hz
F2P             -20.000 ppm
F2            [illegible] Hz
PPMCM          12.00000 ppm/cm
HZCM          9[illegible] Hz/cm
```


back(2)
%Transmittance
Wavenumber
100
90
80
70
60
50
40
30
20
10
0
3800
3600
3400
3200
3000
2800
2600
2400
2200
2000
1800
1600
1400
1200
1000
800
600
O
127
2174.072 1285.410
1664.376 1025.155
1617.736 212.113
1357.950 307.396
1241.606 1552.514
962.477 767.220
815.747 619.914

File : C:\MSDChem\1\DATA\WTS-3-035-2.D
Operator : wts
Acquired : 18 Mar 2008 14:46 using AcqMethod CGCGROUP.M
Instrument : GCMS
Sample Name: wts-3-035-2
Misc Info :
Vial Number: 1





263

125

Current Data Parameters

NAME	wts-2-016#2
EXPNO	20
PROCNO	1

F2 - Acquisition Parameters

Date_	20070802
Time	16.28
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	16
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	724.1
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

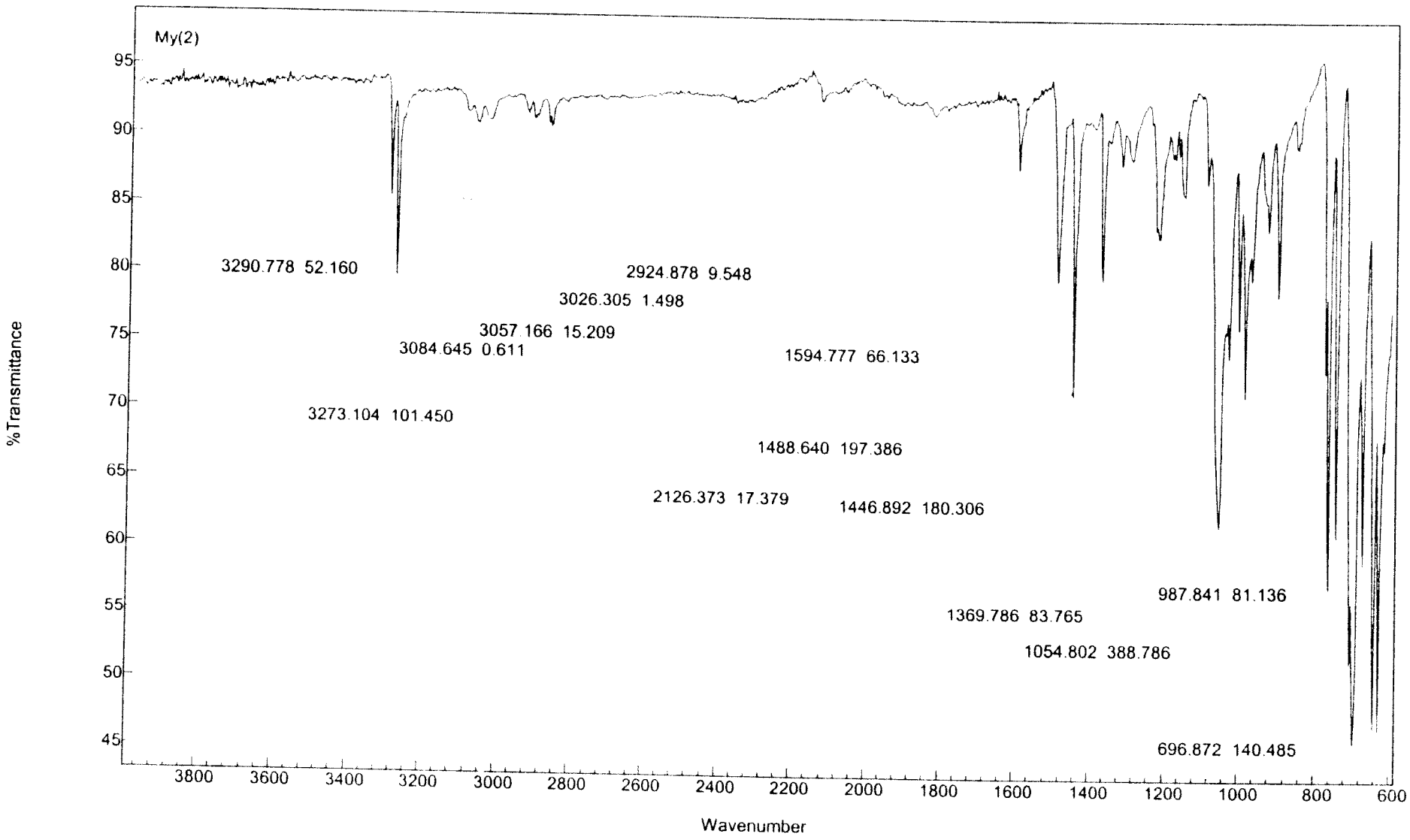
F2 - Processing parameters

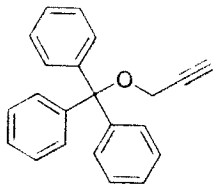
SI	32768
SF	300.1300056 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

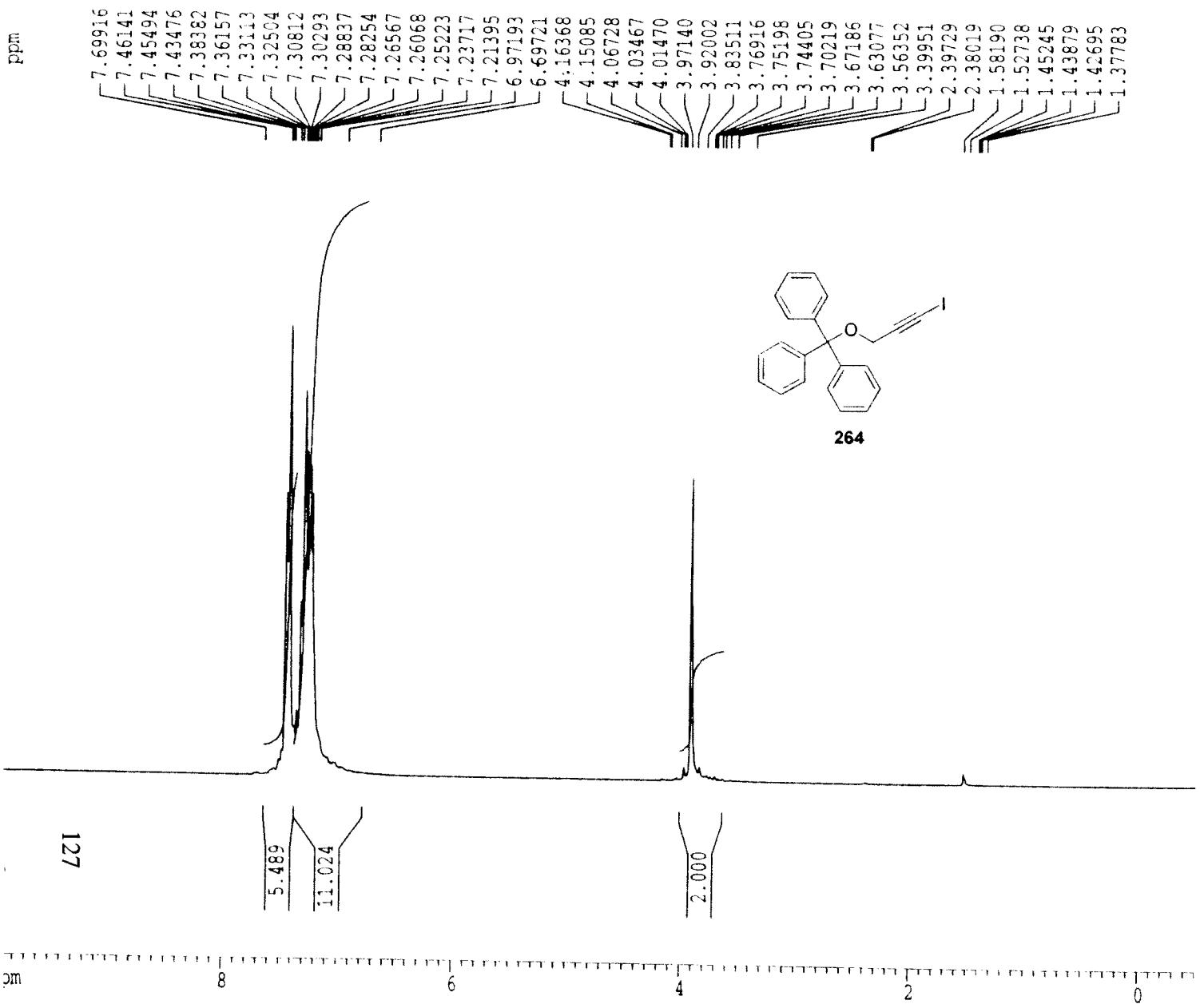
CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

wts-2-016#2





263



Current Data Parameters

NAME	wts-2-022#2rec
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20080104
Time	20.21
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	456.1
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

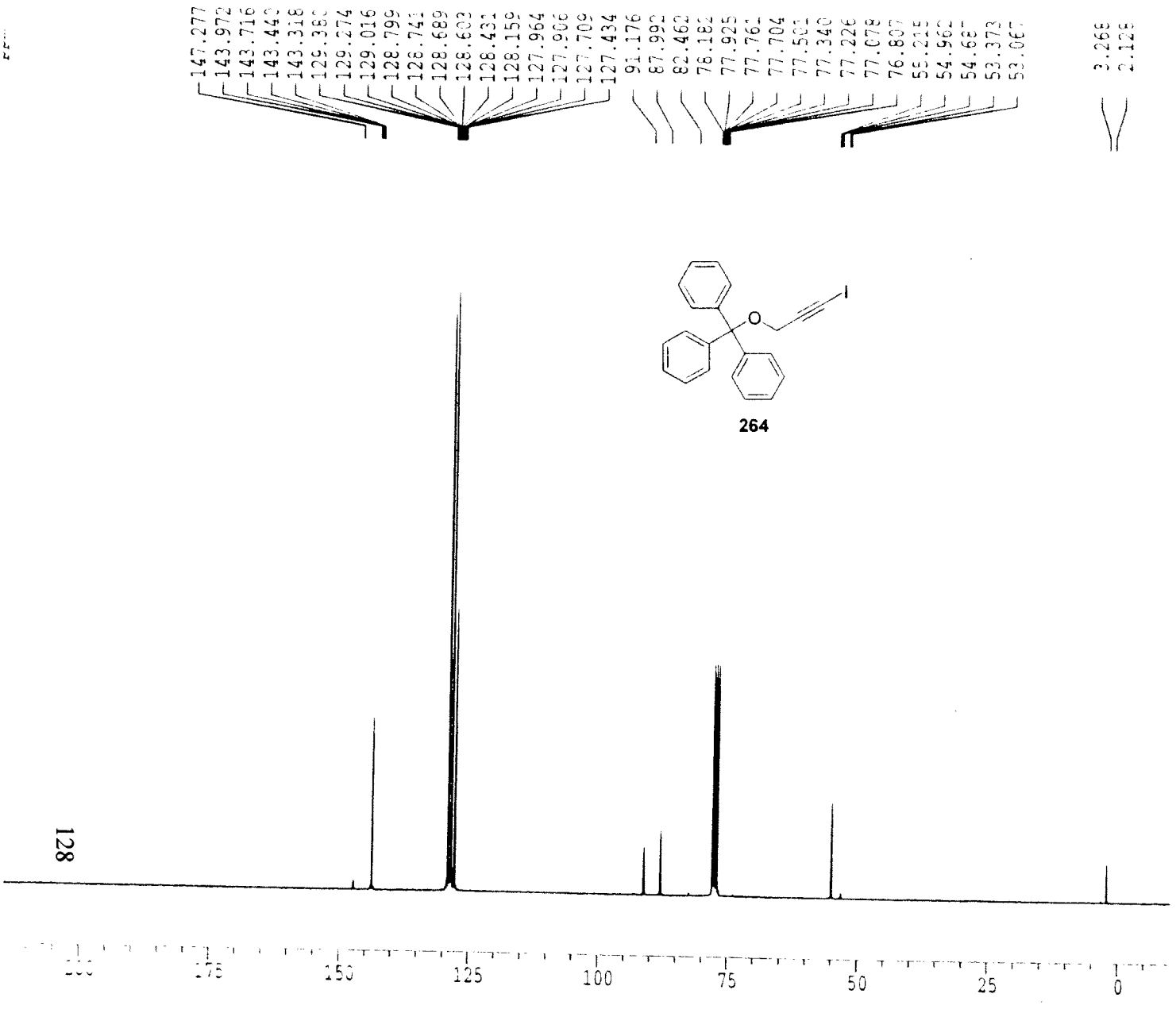
NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300100 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm



Current Data Parameters
NAME wts2022-2c13-9
EXPNO 5
PROCNO 1

F2 - Acquisition Parameters
Date_ 20x03...4
Time ...3e
INSTRUM spect
PROBHD 5 mm ...NF ...1H
PULPROG zgpg30
TD 65536
SOLVENT CDCl3
NS 5000
DS 2
SWH 18832.393 Hz
FIDRES 0.287360 Hz
AQ 1.7400308 sec
RG 2048
DW 26.550 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec
D11 0.03000000 sec
D12 0.00002000 sec

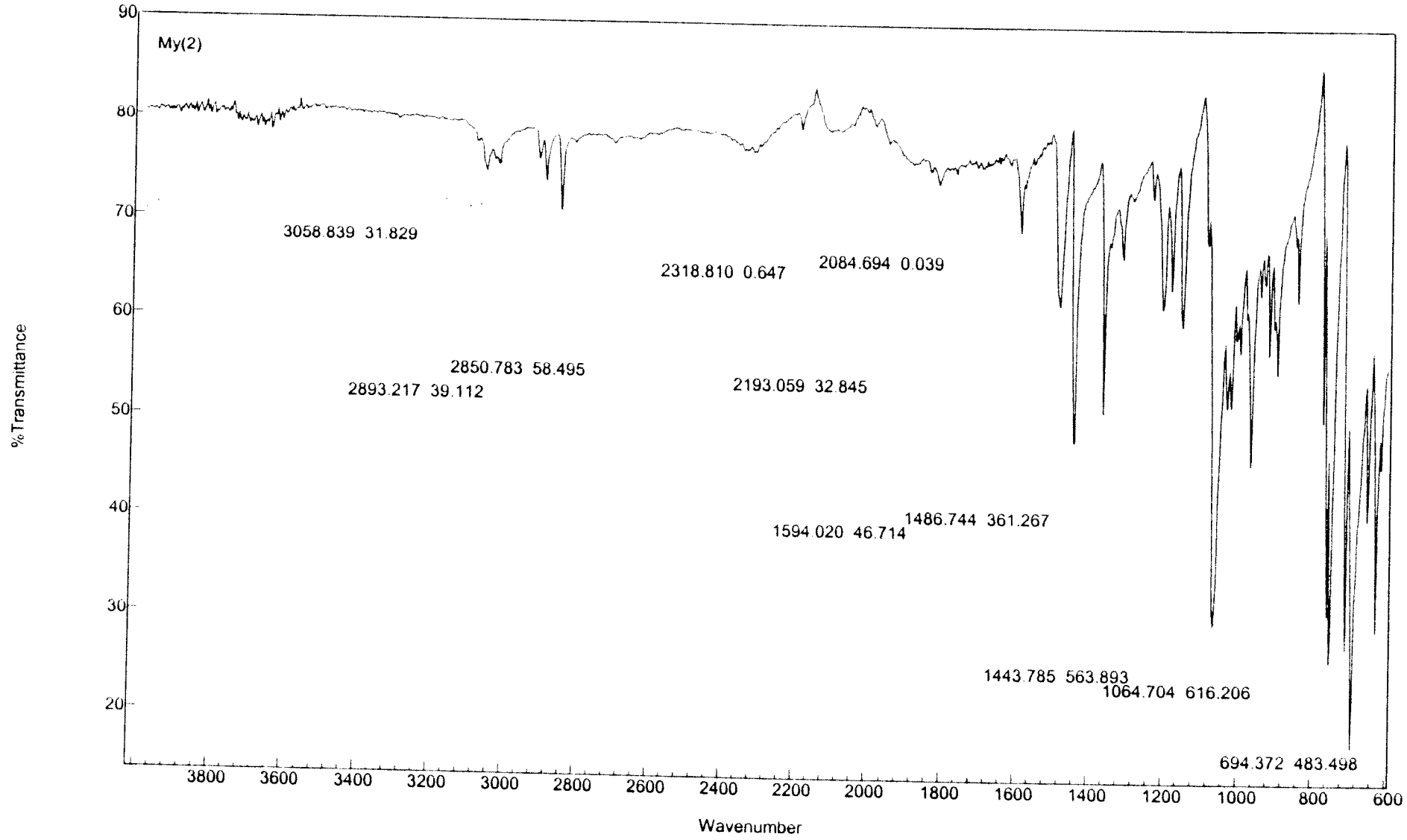
========== CHANNEL f1 ==========
NUC1 13C
P1 ...0 usec
PL1 ...00 dB
SFO1 75.4...0200 MHz

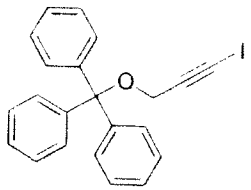
========== CHANNEL f2 ========
CPDPRG2 waltz16
NUC2 1H
PCPD2 ...00 usec
PL2 ...00 dB
PL11 ...00 dB
PL13 ...00 dB
SFO2 300.1311005 MHz

F2 - Processing parameters
SI 32768
SF 75.4677190 MHz
WDW EM
SSB 0
LB ...10 Hz
GB 0
PC ...40

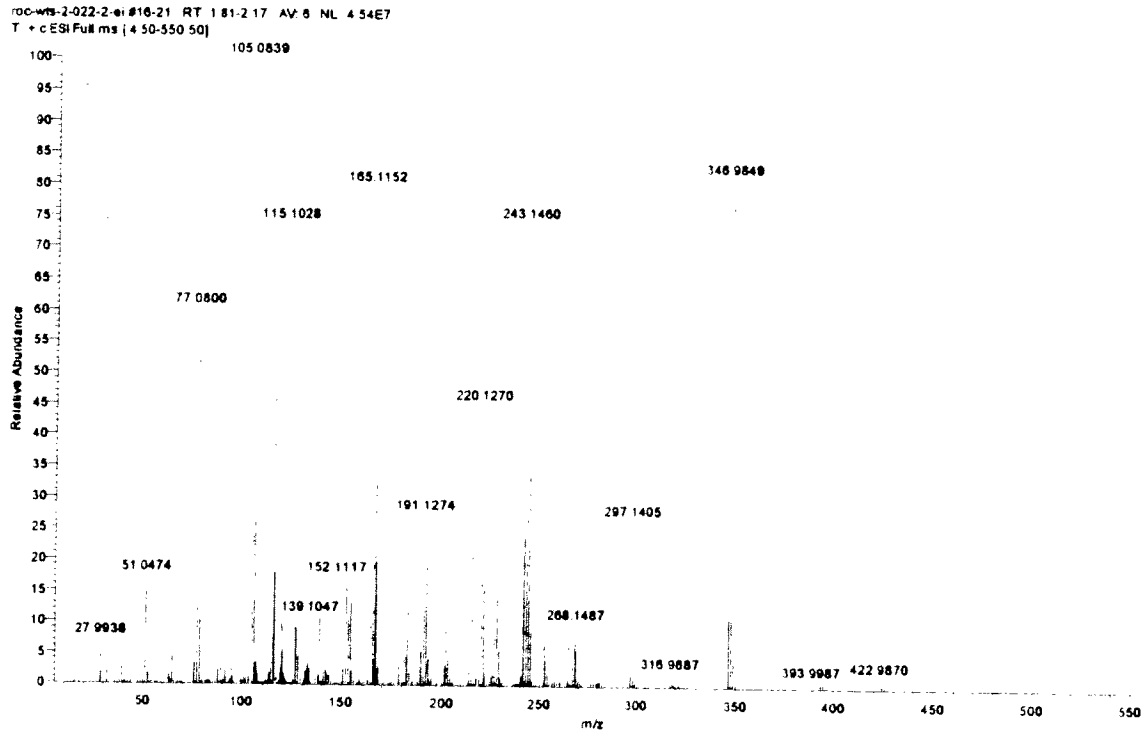
1D NMR plot parameters
CX ...00 cm
F1P ...0.000 ppm
F1 ...2.93 Hz
F2P ...0.000 ppm
F2 ...8.68 Hz
PPMCM 11.50000 ppm/cm
HZCM 867.87878 Hz/cm

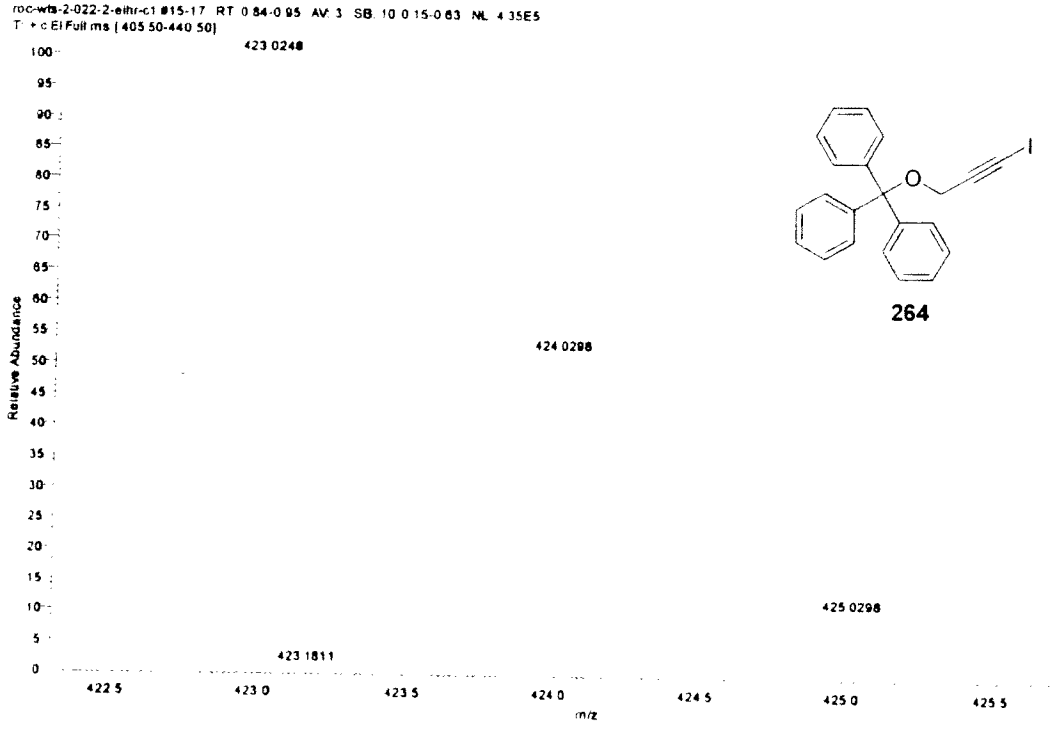
WTS-2-022#2





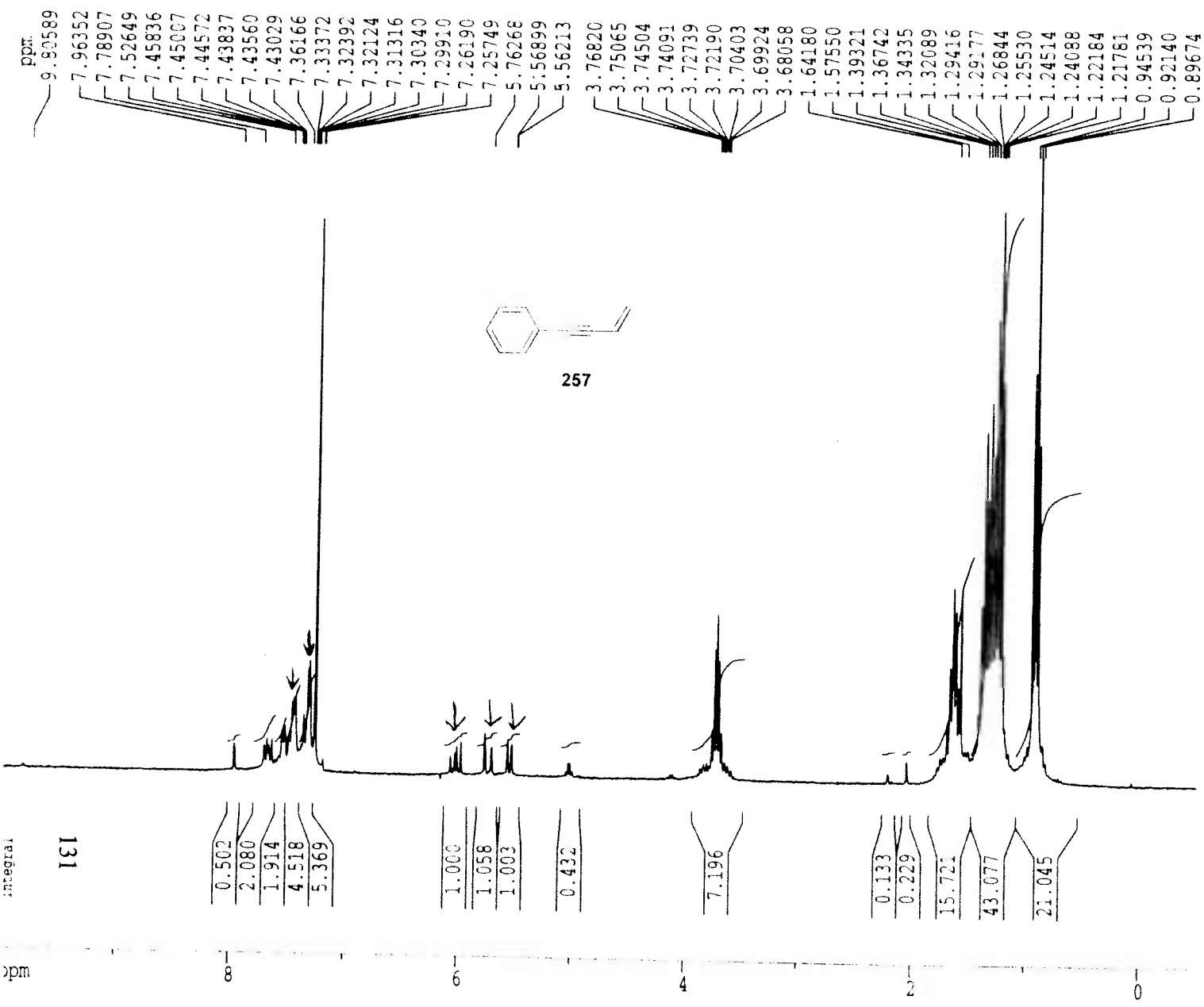
264





264

Mass	Relative Intensity	Theoretical Mass	Delta [ppm]	Delta [mmu]	RDB	Composition
424.02979	52.0	424.0319	-4.9	-2.1	14.0	<<C22 H17 O1 I1 >>



Current Data Parameters

NAME	wts-1-149#1
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20070719
Time	18.01
INSTRUM	spect
PROBHD	5 mm QNP 1H
PULPROG	zg30
TD	65536
SOLVENT	CDCl3
NS	32
DS	2
SWH	6172.839 Hz
FIDRES	0.094190 Hz
AQ	5.3084660 sec
RG	645.1
DW	81.000 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	9.50 usec
PL1	-3.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	32768
SF	300.1300062 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

1D NMR plot parameters

CX	20.00 cm
F1P	10.000 ppm
F1	3001.30 Hz
F2P	-0.500 ppm
F2	-150.07 Hz
PPMCM	0.52500 ppm/cm
HZCM	157.56825 Hz/cm

File :C:\MSDChem\1\DATA\WTS-1-149-1.D
Operator : wts
Acquired : 19 Jul 2007 16:07 using AcqMethod SPENCER.M
Instrument : GCMS
Sample Name: wts-1-149-1
Misc Info :
Vial Number: 1